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Original Articles

CORRELATION OF CLINICAL AND AUTOPSY FINDINGS IN 176 CASES OF ASTHMA

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THE material for this study was obtained from an examination of the records of 176 hospitalized patients who died. These individuals had asthma at the time of hospital treatment as the primary or contributory cause of illness (94 cases), or gave a history of having had it in the past (82 cases). Of these, 153 were treated at the Strong Memorial and Rochester Municipal Hospitals and 23 at the Rochester General Hospital. Autopsy studies were made on 132.

The clinical criteria on which the diagnosis of asthma was based were (1) a history of recurrent, periodic episodes of dyspnea, occurring independently of exertion, or respiratory tract infection, or obvious gross abnormalities of the lungs or circulatory systems; (2) complete or partial relief from dyspnea between the attacks; (3) the presence of wheezes and sibilant and sonorous râles in the chest during the attacks of dyspnea; and (4) partial to complete relief of dyspnea by the administration of epinephrine. Of these criteria, the history of past attacks is considered to be of even greater significance than the physical findings in a single episode of dyspnea.

Many studies of the pathological changes in the pulmonary tissues of individuals who have died of asthma have been reported.[1-11] There is general agreement that the presence of thick, tenacious material in the lumina of the tubes and edema and swelling of the mucosa and submucosa are the most important causes of bronchial and bronchiolar obstruction. There is controversy as to whether constriction of the tubes by the circular muscles of the bronchi contributes to the reduction of the size of the air passages. In the routine autopsy reports on which this study is based, only a few sections from each lung were studied microscopically. Therefore, there is insufficient evidence to warrant any conclusions on this latter problem.

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Fig. 1 is a picture of the lung of a boy, 1½ years old, who had had several severe bouts of asthma and died in an attack. Skin tests with foods and inhalants (Dr. Jerome Glaser) were negative.

When the chest was opened the lungs were seen to be much distended. Areas of marked emphysema appear in the upper and lower lung fields. Between these is a portion of the lung which is atelectatic. The most striking thing about this specimen is the plugs of mucus which fill the bronchi.

Fig. 2 is a picture of the lung of a woman, 65 years old, who also died in an asthmatic attack. She had had periodic attacks of asthma since childhood, rather mild until 3 years before death when they occurred with increasing frequency and severity. She was too sick when admitted to the hospital to permit allergy studies. Her lungs were also much distended. The bronchi were occluded by mucous plugs of the same type as in the child's lung. The whole lung was atelectatic except a small fringe of dilated air sacs at the periphery.

Fig. 1.—Lung of boy, aged 1½ years, dying during an asthmatic attack.

Obviously the same pattern of bronchial obstruction occurred in the young child and the elderly woman.

The amount of mucoid secretion in the bronchi of patients who died in asthmatic attacks varied from quantities which completely plugged even some of the larger bronchi to almost none in a few cases. It was also noted that some of the individuals who died of intercurrent disease or injury, with no asthma at the time, had larger quantities of this secretion than is commonly found in the bronchi in nonasthmatics.

In medical literature, the term "bronchoconstriction" is frequently used to indicate the cause of the obstruction to the passage of air through the bronchial tubes in asthma. It would seem that "bronchial obstruction" is a preferable term in that its meaning can take into account several obstacles which

TABLE I

Number of Deaths of Patients Who Had Asthma at Time of Examination or by History		176
Males (Average Age at Death—54.5 Years) Spread—5 Months to 79 Years	120	
Females (Average Age at Death—55 Years) Spread—6 Months to 86 Years	56	
Autopsies		132

may contribute to the reduction of the lumina of the tubes, whereas the word "constriction" suggests that the sole cause is a squeezing in by some outside force.

Fig. 2.—Lung of woman, aged 65 years, who died during an attack of asthma.

In this study there were 120 males and 56 females. A preponderance of males has been noted in the studies by Lamson and Butt[6, 7] and Schiller, Colmes, and Davis.[12] In general, asthma occurs with equal frequency in the two sexes.

TABLE II

Discharges From Strong Memorial and Rochester Municipal Hospitals, 1926-1951	332,233
Number of Patients With Diagnosis of Asthma as Primary or Contributory Cause of Illness or by History	1,735
Died	153
Autopsies, 1926-1951	13,400
Number of Autopsies on Patients who Died With Asthma as Primary or Contributory Cause of Death	116

The reason for the much greater death rate among male asthmatics is not obvious. It is not explanable on the basis of relative numbers of the sexes admitted to the hospitals because there the ratio in patient population is 3 females to 2 males. It is possible that more males than females have the onset of asthma after the age of forty, but no statistics on this have been found. There was no significant difference in the age at death. In this group there seems to be a partial explanation in the greater frequency of death from coronary artery disease among males (13 males and two females), and in arteriosclerotic heart disease (17 males and 7 females).

The frequency of death from asthma is not known but a rough esitmate of its occurrence in hospitalized patients can be made from the records of the Strong Memorial and Rochester Municipal Hospitals.

TABLE III. RELATION OF AGE OF ONSET TO DURATION OF ASTHMA

Number of Patients Whose Asthma Began in First 5 Years	13
Duration in 6 Cases, ¼ to 1 Year	
Duration in 4 Cases, 7 to 11 Years	
Duration in 3 Cases, 70 to 82 Years	
Average Duration of Asthma With Onset Between 6 and 10 Years	48 Years
Average Duration of Asthma With Onset Between 11 and 20 Years	37 Years
Average Duration of Asthma With Onset Between 21 and 30 Years	23 Years
Average Duration of Asthma With Onset Between 31 and 40 Years	16 Years
Average Duration of Asthma With Onset Between 41 and 50 Years	8 Years
Average Duration of Asthma With Onset Between 51 and 60 Years	8 Years
Average Duration of Asthma With Onset After 60 Years	5 Years

There were more "discharges" than individual patients, because some were admitted more than once.

The incidence of asthma in the general population has been estimated at from 1 to 3 per cent. Its occurrence rate of 0.5 per cent in this group indicates that only the most severe attacks cause patients to be hospitalized. The death rate of hospitalized asthmatics (about 9 per cent) attests to the severity of the illness in these individuals.

The age of onset of asthma in 500 patients seen in routine private and clinic practice conforms with other studies, with the peak of the incidence curve in the first decade and a gradual fall to the seventh. In the patients who have died, the high points of the curve come much later—in the fourth, fifth, and sixth decades. Similar curves have been noted by Lamson and Butt[6] and by Rackemann.[11]

Many of the patients in this group had no allergy studies because they were not seen prior to their terminal illnesses. However, of those who did have such studies, positive skin tests with extracts of foods and inhalants were rarely obtained on patients whose asthma began after the age of forty. Furthermore, of those who died of asthma in childhood or young adult life, specific sensitivity to the common allergens was much less common than in asthmatics seen in routine practice.

In other studies[1-11, 13] of deaths from asthma, a large majority of the patients showed no evidence of specific sensitivity to foods or inhalants by skin tests or elimination trials.

Frequently, the histories noted that the older patients had had asthma in childhood or young adult life from known sensitivity to foods or inhalants. Following periods of freedom of varying lengths, asthma, not related to the original sensitivity, had recurred.

In only 4 of this group of 176 patients did demonstrable specific sensitivity seem to be an important factor in causing death.

Three of these had had asthma for some years only during the ragweed pollen season, but for varying periods before death, asthma had occurred throughout the year, although it was most severe in the ragweed season. They all died in mid-September during severe asthmatic attacks. The fourth patient had asthma only at this season, and dropped dead beside her bed during an asthmatic paroxysm.

So far as could be determined drug allergy was not a factor in any case.

A history of past or present disease of the nasal accessory sinuses was recorded in only 12 cases. It is probable that this is much below the actual occurrence rate and reflects the fact that many of these patients were too sick, when they entered the hospital to make adequate studies possible. The sinuses were not examined at autopsy.

Bronchiectases were found in nine cases.

A satisfactory history relative to familial allergy, especially in the older patients, was unobtainable. The statement from a few patients that a parent or sibling had begun to have asthma in middle life, like themselves, may be significant.

The duration of asthma was measured from the first attack and obviously does not take into account the frequency or severity of the attacks.

In slightly more than half of these patients death occurred within ten years after the onset of asthma, and in one-fifth, within five years. Most of these cases were individuals whose asthma began after the age of forty, but it is noteworthy that six patients died under five years of age. It is also significant that in spite of having had recurrent bouts of a severely disabling disease, nearly half of these patients lived well into the seventh, eighth, and even ninth decades.

It was surprising to find that 6 of 13 individuals whose asthma began very early in life died in less than one year after the onset, all in asthmatic attacks. None of these showed specific sensitivity to foods or inhalants. On the other hand three patients whose asthma began at the same age, in whom specific sensitivity could be demonstrated, lived to advanced years and died of some condition other than asthma. Of the middle group of four, one died of mitral heart disease, one of pneumonia, while the other two died of asthma for which no specific cause could be assigned.

The relatively long duration of asthma beginning in childhood and young adult life fits into the usual conception that this disease is benign so far as danger to life is concerned, in spite of the great suffering and disability which it causes.

The rapid drop in the length of life of patients whose asthma started after the age of forty suggests that this type of asthma presents a much more serious hazard than that which begins in youth. This seems directly related to the fact that such complications as pulmonary emphysema and fibrosis and heart disease tend to become more frequent in later life, as does the susceptibility to serious respiratory tract infections.

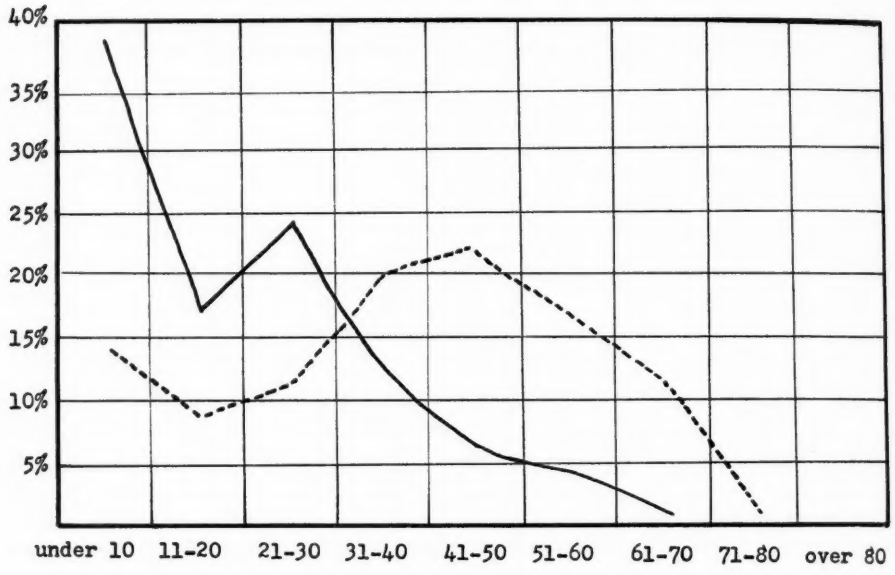

Fig. 3.—Age of onset of asthma in living asthmatics, and in asthmatics who died.
——— Age of onset in 500 patients.
------ Age of onset in 176 patients who died.

Ninety-four patients died during attacks of asthma.

In those who by clinical standards died because of asthma, the disease followed a typical course. After periods of uncontrollably severe dyspnea, with increasing cyanosis and coma, there was gradual cessation of respiration and heart beat. It seems logical to conclude that the body mechanism ceased to function because the organs received inadequate supplies of oxygen. In all, the bronchial mucosa was swollen and edematous, and the lumina of the bronchi contained varying amounts of tenacious secretion.

That at least one other factor may play a part is suggested by observations of the gases of the arterial blood of two patients a short time prior to death. The CO_2 content was 86 and 85 volumes per cent and the oxygen saturation 71 and 73 per cent. Such a finding makes it necessary to consider an uncompensated gaseous narcosis as well as the obvious anoxia.

Hurtado and his associates[14] have shown that high values of carbon dioxide in the arterial blood are found regularly in association with a marked increase in the ratio of residual air to the total pulmonary capacity. Studies of the lung volume in some of these patients at times when they were not having

severe asthmatic attacks showed that the residual air exceeded 55 per cent of the total capacity. It is probable that this increase was even greater during severe asthma.

Baldwin and her associates[15] note that the CO_2 retention resulting from hypoventilation tends to produce mental confusion and even coma.

In four instances large areas of atelectasis were found in the lungs. In several others, small atelectatic areas were noted on microscopic examination. It is probable that these airless regions furnished fertile soil for the growth of bacteria and their presence may account for the frequency with which bronchopneumonia occurred in these cases.

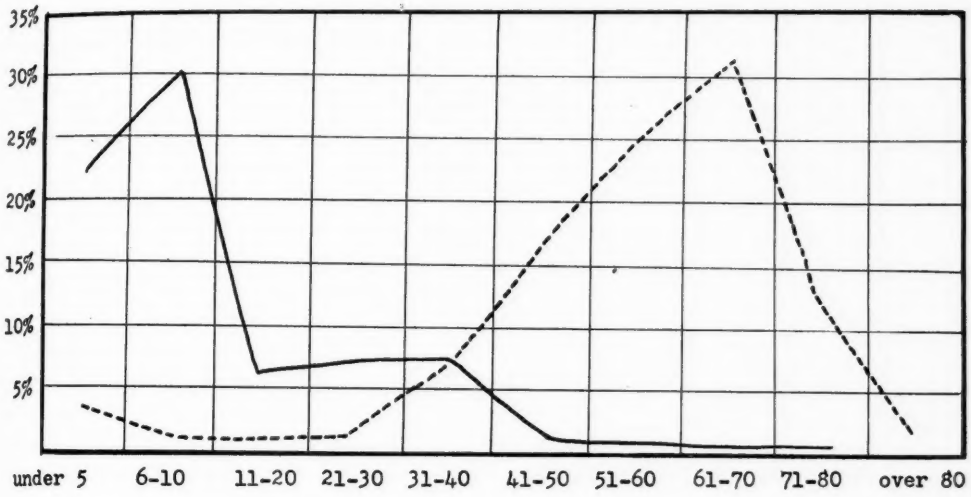

Fig. 4.—Duration of asthma and age at death.
——— Duration of asthma in 176 patients who died.
------ Age at death.

In 35 cases pneumonia and heart disease seemed, from the clinical viewpoint, to be the major causes of death. Because of the well-known tendency of respiratory tract infections to produce exacerbations of asthma, it is not surprising that extreme dyspnea should be present in the patients who had pneumonia. The five patients who died of congestive heart failure (average age, 56 years) had had asthma for many years and all had marked emphysema. The severe asthma in the terminal attacks may logically be assumed to have put intolerable burdens on already damaged hearts.

It was not possible to determine whether the asthmatic attacks were instrumental in precipitating the myocardial infarcts.

Asthma was not present in the terminal illnesses of eighty-two patients. Pulmonary infections and heart disease were the major causes of death. Of the cases of pneumonia, all except two occurred in patients past middle life.

Cardiac hypertrophy, with or without dilatation, was found in 54 of the 132 autopsied cases. In all but 6, asthma had been present for at least five

TABLE IV. CAUSES OF DEATH IN PATIENTS DYING IN ASTHMATIC ATTACKS

Number of Patients Who Died in Asthmatic Attacks	94
Number of Patients Who by Clinical Standards Died Asthma Deaths	59
Causes of Death Other Than Asthma	
Congestive Heart Failure	5
Bronchopneumonia (2 Cases of Bronchiectasis)	19
Lobar Pneumonia	3
Myocardial Infarct	5
Acute Fibrinous Pericarditis	1
Mitral Stenosis and Insufficiency	1
Coarctation of Aorta and Patent Ductus Arteriosus	1

years, and, in most instances, much longer. In the 6 cases with asthma of shorter duration, episodes of severe dyspnea had recurred frequently for two to four years.

All had marked emphysema and, in many, fibrotic changes in the lungs were noted. Atheromatous and sclerotic processes in the pulmonary arteries were common.

No studies of the pulmonary blood pressure were made. The systemic blood pressure readings were in the low normal range in most instances. Only about one-half dozen records of systolic pressures in excess of 200 mm. mercury were found. The three cases of left ventricular hypertrophy were among these.

Evidence of damage to the right heart is to be expected in individuals with this type of pulmonary pathology. Finding so many instances of hypertrophy and dilatation of both chambers was surprising, especially so, in individuals who showed no evidence of abnormal resistance to blood flow in the systemic circulation. Baldwin and her collaborators[15] suggest that such left heart damage may result from anoxia.

An increase in hemoglobin and the number of red blood cells is regularly found in people who are exposed to low barometric pressures. One would expect to find a similar increase in these individuals who showed a degree of anoxia comparable to inhabitants of high altitudes. However, this was not the case. With but a few exceptions, the number of erythrocytes and the hemoglobin values were not above normal and, indeed, many had mild to moderate anemia. The few exceptions occurred in individuals who showed evidence of chronic congestive heart failure.

TABLE V. CAUSES OF DEATH IN PATIENTS WHO DID NOT DIE IN ASTHMATIC ATTACKS

Broncho-Pneumonia	11
Lobar Pneumonia	10
Pulmonary Emboli	4
Arteriosclerotic Heart Disease	24
Myocardial Infarction	10
Cancer	8
Diabetes	2
Periarteritis Nodosa	1
Cerebral Hemorrhage	3
Nephritis	3
Ruptured Abdominal Viscus	3
Accident	3
Total	82

TABLE VI. CARDIAC HYPERTROPHY IN 132 AUTOPSIED CASES

Right Heart Hypertrophy and/or Dilatation	40 Cases
Right and Left Heart Hypertrophy and/or Dilatation	11 Cases
Left Heart Hypertrophy	3 Cases
Average Age, 55½ Years	
Spread, 32-80 Years	

The question as to whether or not asthma damages the heart is frequently asked. There is some evidence that asthma, alone, does not present a serious hazard. (1) The patients whose asthma began prior to the age of 40 lived nearly the average life span. It is not conceivable that they would have done so if their hearts had suffered severe injury. (2) Electrocardiographic reports of no abnormal findings, and measurements of the heart shadows within normal limits on the x-ray pictures were noted repeatedly in the records of patients who were studied at intervals over several years. (3) The common knowledge that death from asthma is rare seems to confirm this impression; however, if marked emphysema develops in the asthmatic, the story is different. Cournand[16] has shown that such a chronic pulmonary disease, with its reduction in the pulmonary vascular bed, and the resultant anoxia, leads to pulmonary hypertension with right heart hypertrophy and ultimate dilatation and failure.

In addition, Prinzmetal and Kountz[17] have shown that there is a rise in the negative intrapleural pressure with a concomitant rise in the negative pressure in the pericardial sac in asthma and emphysema, resulting in circulatory disturbances.

It would seem, therefore, that this question must be answered in two ways: (1) Asthma alone does not commonly damage the heart, but, (2) if severe emphysema develops, heart injury is likely to result.

Morphine was used sparingly in this group of patients. In one case of massive atelectasis, morphine seemed to have depressed the cough reflex so much that he was unable to expel the mucous plugs. However, he had been given many previous doses of this drug, sometimes enough to depress his respirations to six per minute without trouble.

In two other cases, morphine was administered after other methods of treatment had failed to relieve extremely severe dyspnea. These patients died quietly during the resulting sleep.

Two patients whose deaths were caused by coronary occlusion were given epinephrine by injection, twice within two hours preceding deaths. However, no such medication was administered immediately preceding death in the other thirteen patients with this condition, so it is improbable that epinephrine was responsible for the damage.

Naturally, many of these patients had used much epinephrine by injection and inhalation for many years. No pathological findings which could be attributed to such use were observed.

The presence of eosinophilia was unexpectedly low in these patients. In about one-third, no eosinophils were noted in routine blood counts. At the other extreme, counts of 20 to 40 per cent were present in a few cases. In the remainder, values of 2 to 10 per cent were recorded.

In only about one-fourth of the reported cases of death from asthma is there evidence that the asthma was the result of sensitivity to ingestants or inhalants. This gives the impression that "intrinsic" or "bacterial" asthma presents a greater hazard to life. The infrequency with which specific sensitivity could be incriminated in the patients of all ages in this group supports this impression. Two reasons for this difference seem to be: (1) In individuals in whom specific sensitivity can be demonstrated, treatment by elimination of the offending substances or specific hyposensitization can be effected, whereas, in the other group, specific treatment is seldom possible. (2) In the cases of "intrinsic" asthma, there seems to be a greater tendency to develop irreversible changes in the lungs with their serious sequelae.

SUMMARY

1. A study of the records of 176 hospitalized asthmatic patients who died is presented. In 94, asthma was the primary or contributory cause of the terminal illness. Autopsy studies were made on 132.

2. The chief cause of bronchial and bronchiolar obstruction was found to be swelling and edema of the mucosa and submucosa of the bronchial wall plus the presence of varying amounts of thick tenacious secretion in the lumina of the bronchi.

3. There were 120 males and 56 females.

4. Asthma occurred in about 0.5 per cent of the hospital population. The death rate of these hospitalized asthmatics was about 9 per cent.

5. In the majority of the patients, asthma began in middle or late life, but in a few the onset was as early as the first year.

6. Specific sensitivity to food, inhalants or drugs seemed to be an important cause of the asthma in but a very few instances.

7. In about one-half of the patients death occurred within 10 years after the onset of the asthma; in about one-fifth, within five years. Nearly half of the patients lived into their seventh decade or later.

8. As judged by clinical standard, in about one-third of the patients the cause of death was asthma.

9. Pneumonia and heart disease were the causes of death in a majority of the others, whether asthma was present in the terminal illness or not.

10. While extreme anoxia seems to be the chief factor in causing death from asthma, uncompensated gaseous narcosis may play a part in the production of the terminal mental confusion and coma.

11. Hypertrophy of the heart with or without dilatation was found in about one-third of the cases.

12. Evidence that asthma alone does not produce a serious hazard to the heart is presented. However, when emphysema develops, heart damage is likely to follow.

13. Morphine was used so little in these cases that it was not an important factor in causing death.

14. Many patients had used much epinephrine for long periods. No pathologic findings suggestive of injury from this treatment were found.

15. Eosinophilia was less commonly found in these patients than was expected.

CONCLUSIONS

Although death from asthma is uncommon, it does occur in all age groups; more frequently in those patients whose asthma begins in middle life or later.

Asthma resulting from specific sensitivity to ingestants and inhalants is less dangerous to life than is the "intrinsic" or "bacterial" variety.

Asthma alone does not present a serious hazard to the heart, but when irreversible changes in the lungs, such as emphysema, occur, heart damage is likely to result.

The long-continued use of epinephrine by injection and inhalation produced no recognizable pathological changes in these patients.

The author wishes to express his thanks to the members of the Departments of Pathology for making the autopsy protocols available and for much helpful advice, and to the members of the clinical records department, and to Mrs. Olga Nell for much assistance.

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DEATH OCCURRING IN BRONCHIAL ASTHMA
A REPORT OF FIVE CASES

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IN THE period from Jan. 1, 1948, through June 30, 1949, this hospital has recorded the discharge of 290 patients with a primary or secondary diagnosis of bronchial asthma. In this group there were 17 deaths. Of the group of 17, death was due primarily to asthma in 5, a percentage of 1.7. Four of these patients were autopsied. A fifth patient died Sept. 15, 1951, and was autopsied. Because of the high percentage of asthmatic deaths in this group an examination of the circumstances of death and the type of care is felt to be of value. It should be pointed out that many patients with chronic, intractable pulmonary disease are advised to come to Arizona for climatologic relief and all of the cases to be described below were thus referred to this section of the country.

Bronchial asthma is defined as dyspnea of a "wheezy" type with prolonged expiratory phase, occurring paroxysmally.[1] The term asthma has been loosely applied and, as pointed out by Lamson and Butt,[2] a diagnosis of asthma has been made in patients with wheezing respiration, paroxysmal or continuous, based on heart disease, pneumoconiosis, renal disease, pulmonary fibrosis, tracheal obstruction, and distortion of the thorax. It is important to separate such cases from those of true bronchial asthma which are divided by Rackemann into the extrinsic or allergic, and the intrinsic type.[3] The diagnosis must be based on the clinical history, physical findings and characteristic pathology. The pathological pulmonary changes described as characteristic[4, 8, 9] are: (1) thickening and hyalinization of the basement membrane of the bronchial epithelium, (2) variable numbers of eosinophils in the cellular exudate which may be present in the bronchial wall, around the glands and in the mucus in the lumen, (3) excessive luminal mucus, frequently with Charcot-Leyden crystals and Curschmann spirals, (4) mucinous degeneration of the bronchial epithelial lining, (5) hyperplasia and mucinous degeneration of the mucus glands, (6) hypertrophy of the muscular layer of the bronchi, (7) dilatation of the bronchioles and alveoli, (8) widening of the submucosal layer and thickening of the vessel walls, and (9) mucus plugs in most of the smaller bronchi. This last finding seems well established as the cause of death in most patients dying in an asthmatic paroxysm as described by Mallory.[1]

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Hilding,[5] in a consideration of 39 fatal cases of asthma, emphasized the marked alteration of the bronchial lining with replacement of the normal columnar epithelial cells by goblet cells. He felt that loss of normal ciliary motion, combined with the production of viscid mucinous secretion, combined to produce the fatal plugging of the small bronchi. The importance of morphine in contributing to death from asthma is emphasized by Vaughn[6] and Unger.[4] Of the 7 fatal cases reported by Thieme,[7] morphine was implicated in 3; morphine had been administered in 5 of the 7 patients reported by Craige,[8] and of the 27 cases reported by Rackemann,[1] several had had morphine. Rackemann[3] reported 27 cases dying of asthma and reviewed 55 cases from the literature up to 1944. He pointed out the great majority of fatal cases occurred in patients with onset of asthma between 40 and 50 years of age in whom the disease was progressive, and in several of whom the course was quite short, sometimes only a few months or years (2-5). These are the cases which he calls intrinsic asthma and in which an allergic etiology is not very convincing. The occurrence of emphysema in the fatal cases of asthma is practically universal.

CASE REPORTS

CASE 1.—G. D. P. This 61-year-old white male was admitted to the hospital on May 17, 1949. He had a history of asthma for 4 or 5 years and was transferred from the Navy Hospital, Mare Island, Calif., to this hospital. His chief complaints were shortness of breath, productive cough and rhinorrhea, and he stated that he had an allergy to aspirin. Physical examination on admission revealed a well-developed, poorly nourished white man, 5 feet 8 inches tall, and weighing 128 pounds. The chest expansion was limited and the AP diameter of the chest was increased. The chest was resonant and breath sounds were distant. A few wheezes were heard bilaterally. An allergic rhinitis was noted. The blood pressure was 150/88. Urinalysis was negative. Red count and hemoglobin were within normal limits; the white count was 7,300 with 9 per cent eosinophils. X-ray of the chest was normal except for emphysema. The electrocardiogram was normal.

During hospitalization the patient received 0.2 Gm. doses of aminophylline, 25 mg. of ephedrine, and 0.6 Gm. of potassium iodide; these medications were given 3 times a day. Adrenalin (1-1000) was given in 0.25 ml. doses as needed. He also received 50 mg. of Benadryl 3 times a day from June 15. The patient was fairly comfortable but attacks of asthma did occur at night and in the early morning. Adrenalin in oil was accordingly given at night and on occasion he received intravenous aminophylline. On the evening of July 14, patient received 1 ml. of Adrenalin 1-500 in oil at 9:30 P.M.; at 9:45 he complained of continued dyspnea and was given 0.5 ml. of Adrenalin subcutaneously. He continued to be quite dyspneic and suddenly became cyanotic. Ten grains of aminophylline were given intravenously at 9:56 P.M. and the patient died at 10:00 P.M. His condition had become alarming only in the ten minutes before death.

Post Mortem Examination.—Examination done July 15, 1949, revealed the following pertinent findings. The left lung weighed 370 grams and the right 420 grams. The lungs were voluminous and did not collapse on opening the chest. The major bronchi were very thick walled with small lumina occluded by thick tenacious opalescent mucus. Obstruction and thickening of bronchi began within 1 cm. of origin of individual branches and extended well out into the lung tissue, and were still grossly visible in bronchi of 2 mm. diameter. There were no areas of atelectasis or consolidation. The pulmonary vessels were patent with pale, smooth intima.

The right ventricle was 5 mm. in thickness. The heart weighed 400 grams. A moderate degree of atheroma of coronaries with small areas of calcification was noted.

Fig. 1.

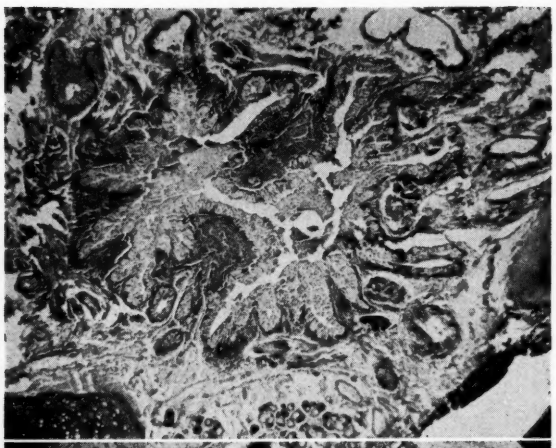

Fig. 2.

Fig. 3.

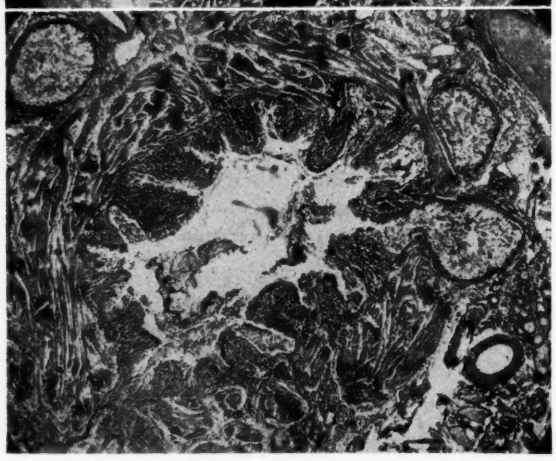

Fig. 1.—Case 1. Small bronchus showing lumen filled with mucus, muscular hypertrophy, and thickening of bronchial wall. Spasm of muscle appears to be present.

Fig. 2.—Case 2. Small bronchus. Same appearance as Fig. 1.

Fig. 3.—Case 3. Small bronchus. Same appearance as Figs. 1 and 2.

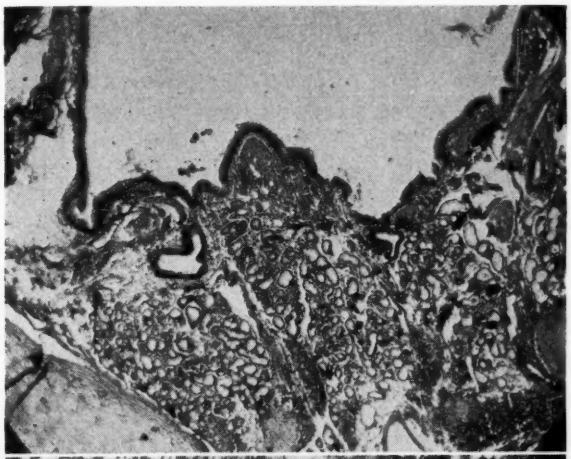

Fig. 4.

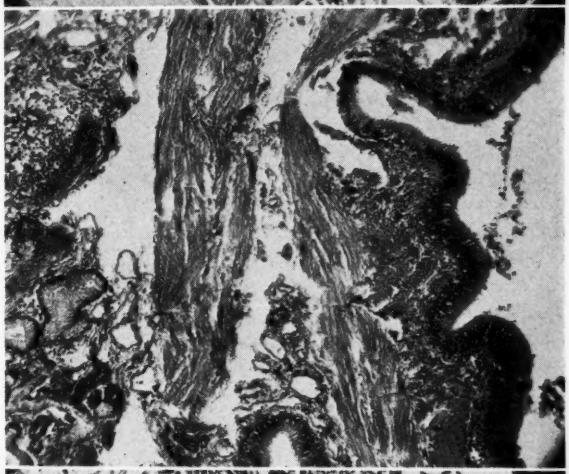

Fig. 5.

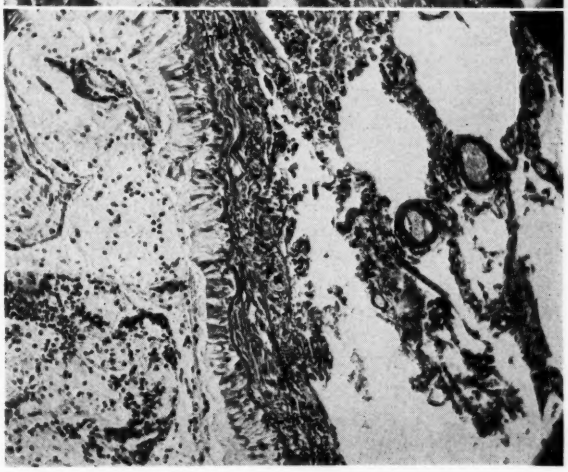

Fig. 6.

Fig. 4.—Case 4. Medium-size bronchus. Thickening of wall by muscular hypertrophy and glandular hyperplasia. Obstructing mucus absent.

Fig. 5.—Case 4. Higher power of bronchus in Fig. 4, showing muscular hypertrophy and cellular infiltration.

Fig. 6.—Case 3. Small bronchus showing exudate mucus in lumen, and epithelial change. Pulmonary vessels are thickened.

Microscopic Examination.—The bronchi showed marked hypertrophy of muscle, and thickened mucosa with severe infiltration of lymphocytes and eosinophils. Hyaline thickening of the basement membrane of the epithelium with slight extrusion into the ducts of the glands was noted. Interstitial infiltration of lymphocytes and eosinophils in glands with evidence of hyperactivity of mucus secreting cells were seen. Squamous metaplasia of bronchial epithelium was noted in some places. The bronchial lumina contained mucus, lymphocytes, eosinophils, and cellular debris. No Leyden crystals or Curschmann's spirals were noted. Cause of death was described as complete obstruction of the bronchial system by mucus.

CASE 2.—T. M. This 53-year-old Negro man was admitted to the hospital on April 23, 1949, for treatment of an asthmatic attack of 1 week's duration. The patient had a history of asthma since 1918 and stated that he was allergic to tomatoes, milk, corn, cereals, dusts, and ragweed. He had had numerous hospitalizations since 1918 and his last hospitalization had been from September of 1948 to January of 1949 at the Tucson Veterans Hospital. He was comfortable from January to April of 1949 on oral medication with Tedral* and aminophylline. Wheezing and shortness of breath became progressively worse for one week before admission. The initial examination revealed a well-developed, poorly nourished, Negro man with slight dyspnea at rest. The AP diameter of the chest was increased. Percussion note was hyper-resonant. Wheezing and dry expiratory râles were noted bilaterally. The blood pressure was 100/70. The pulmonary second sound was considerably louder than the aortic second sound. The heart was otherwise normal to physical examination. The chest x-ray showed pulmonary emphysema and the electrocardiogram was suggestive of right ventricular preponderance. The red count and hemoglobin were normal. The white count was 6,000 with 1 per cent eosinophils. Urinalysis was within normal limits. The patient was placed on spaced dosage of aminophylline, potassium iodide and ephedrine 5 times a day. He was given 0.25 ml. doses of adrenalin 1-1000 as needed. The patient was quite dyspneic for the first week despite this treatment and required intravenous aminophylline which was given in 5 per cent glucose as an intravenous drip on several occasions. The patient then improved and became ambulant. He was able to leave the hospital on overnight passes, and on July 5 was granted a trial leave from the hospital. He continued on the spaced dosage of aminophylline, ephedrine, and potassium iodide. On the morning of July 30, 1949, the patient's wife phoned the hospital stating that he had been short of breath for about an hour. Shortly afterward the patient was brought to the hospital, but was dead on arrival.

Post Mortem Examination.—Examination was performed July 30, 1949. The pertinent findings were a left pneumothorax with collapse of the left lung, except for the upper lobe which was held out by adhesions. The left lung weighed 448 grams and was moderately crepitant and soft. No consolidation was noted. Many small emphysematous blebs and fibrous tags were noted over the apex. The bronchi, especially of the upper lobe, showed thickened walls with reduced lumen and thick gelatinous mucoid material filled the lumina. The right lung weighed 580 grams and thick walled bullae were noted in the apex. The lower lobe was voluminous and did not collapse. Small bronchi throughout the lung were greatly thickened with constricted walls, and those to the lower lobe especially were occluded by thick mucous plugs. The pulmonary vessels showed some fibrosis and atheromatous change.

The heart weighed 380 grams. The wall of the right ventricle was 5 mm. in thickness, and the wall of the left ventricle was 17 mm. in thickness. The coronary arteries and valves were normal.

Microscopic Examination.—The basement membrane of the bronchial epithelium was thick and hyalinized. Occasional areas of squamous metaplasia of bronchial epithelium were noted. The bronchial mucosa was thickened and infiltrated with lymphocytes and eosinophils. The bronchial muscle was greatly hypertrophied and the glands were hyperactive with slight cellular infiltration present.

The immediate cause of death was felt to be acute obstructive emphysema, due to occlusion of the bronchi by mucus plugs. The spontaneous left pneumothorax was not felt by itself to explain the sudden death. Pulmonary arteriosclerosis was present, as was chronic pulmonary emphysema and slight right ventricular hypertrophy.

*A proprietary medication containing phenobarbital, 8 mg.; theophylline, 0.12 Gm.; and ephedrine hydrochloride, 25 mg.

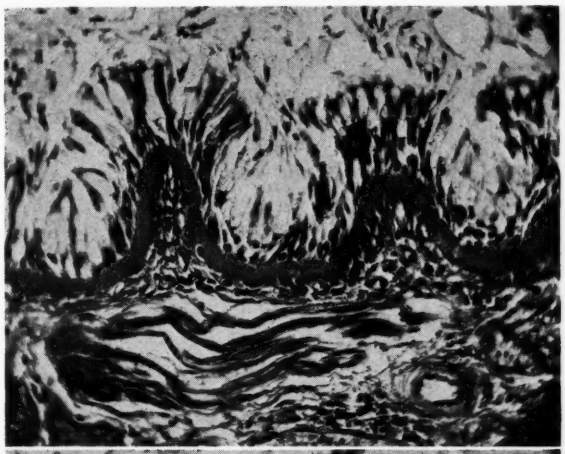

Fig. 7.

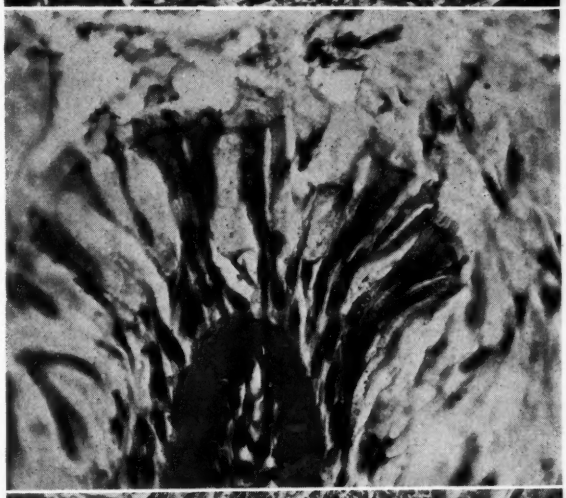

Fig. 8.

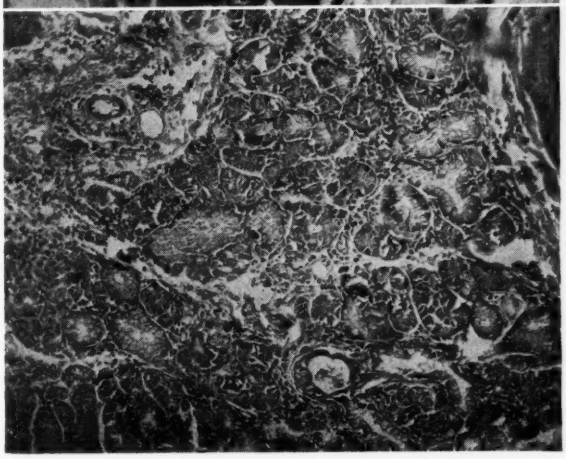

Fig. 9.

Fig. 7.—Case 3. Hyalin basement membrane, presence of goblet cells, loss of cilia and mucinous degeneration in epithelium.

Fig. 8.—Case 3. High power detail of Fig. 7.

Fig. 9.—Case 1. Changes in bronchial glands, showing increased activity, cellular infiltration, and mucinous degeneration.

CASE 3.—E. B. This 53-year-old white man was admitted to the hospital March 8, 1949, with complaints of dyspnea and tightness of the chest. The patient had noted these symptoms for about 4 weeks before admission. His history revealed that he had had asthma for 15 years with numerous hospitalizations. The patient was noted to be acutely ill (cyanotic and dyspneic) on admission. AP diameter of the chest was increased. The lungs were hyper-resonant and numerous wheezes were noted bilaterally. The heart tones were distant and the second pulmonary sound was louder than the aortic second sound. The blood pressure was 100/70. There was no evidence of cardiac failure. The chest x-ray showed pulmonary emphysema and there had been no change in appearance of the chest x-ray since 1947. No electrocardiogram was done on this admission but electrocardiogram in 1947 was normal. Urinalysis was negative. Red count and hemoglobin were within normal limits. The white count was 8,000 with 3 per cent eosinophils. The patient was treated with oral aminophylline, ephedrine, and frequent injections of adrenalin. Intravenous aminophylline was given on the ninth of March. The patient continued to have dyspnea and wheezing and was started on oxygen. He died suddenly on the morning of March 11, 1949.

Post Mortem Examination.—Examination done March 14, 1949, revealed the following pertinent findings. The lungs were voluminous and did not collapse on removal from the thorax. The right lung weighed 600 grams and the left 580 grams. All of the bronchi from about 2 inches beyond the bifurcation were small in diameter, thick walled, and occluded by very thick opalescent mucus which could be expressed with difficulty as semisolid plugs. The process involved all the bronchi bilaterally and resulted in almost complete occlusion of the pulmonary air passages. The pulmonary vessels were patent with smooth intima showing slight atheromatous changes.

Microscopic Examination.—Pulmonary emphysema was evident. The bronchi showed areas of squamous metaplasia of the epithelium with a thick, hyaline basement membrane, widening of the mucosa and infiltration of the mucosa with lymphocytes and eosinophils. The bronchial musculature was markedly hypertrophied. The mucus glands showed evidence of hyperactivity and there was interstitial infiltration in the bronchial glands of lymphocytes and eosinophils. There were masses of mucus containing lymphocytes, eosinophils and cellular debris in the bronchial lumen. Cause of death was noted as acute obstructive emphysema, with obstruction of the entire bronchial system by mucus plugs.

CASE 4.—R. V. M. This 51-year-old white man was admitted to the hospital April 2, 1947. The patient had been discharged as having arrested pulmonary tuberculosis in September of 1946 and had been living in the Domiciliary Barracks here from December of 1946 to April of 1947, when a sputum was noted to be positive for acid-fast bacilli on routine examination. The patient had a history of asthma since 1941. Physical examination on admission revealed the patient to be well developed and fairly well nourished. The AP diameter of the chest was increased and scattered wheezes and dry râles were noted bilaterally. The diaphragms were low and moved poorly, the chest was hyper-resonant, and both cardiac and liver dullness were obliterated by pulmonary resonance. Examination of the heart revealed the pulmonary second sound to be accentuated. The blood pressure was 100/70. There were no evidences of cardiac failure. Urinalysis was normal. Red count and hemoglobin were within normal limits. The white count was 7,000 with 1 per cent eosinophils. The sedimentation rate was 29 mm. per hour (Cutler). The electrocardiogram was interpreted as showing right ventricular preponderance. Chest x-ray showed pulmonary fibrosis and emphysema with honeycombing in both upper lobes. During hospitalization the tuberculosis was considered quiescent as no changes were seen in the serial chest films although an occasional positive sputum was noted. His chief complaints were shortness of breath, wheezing, and occasional febrile episodes. Treatment included Pyrabenzamine and oral ephedrine, aminophylline, and potassium iodide given 4 times a day for control of asthma. On Nov. 29, 1947, low grade fever developed with some increase in sputum and the patient was treated with penicillin. He developed cyanosis, pedal edema, hepatomegaly, and cervical venous congestion, and fluoroscopy revealed dilatation of the heart. He was digitalized, given mercurial diuretics, low salt diet, and oxygen. Evidences of congestive failure were cleared within a

week. Antiasthmatic medication was continued. Following this episode he wheezed only intermittently and did not appear to be in any significant respiratory distress. On Dec. 16, 1948, while sitting at his bedside, he suddenly gasped, became cyanotic, quickly became pulseless with only an occasional gasping respiration, and was dead within 5 minutes.

Post Mortem Examination.—Examination done Dec. 17, 1949, revealed the following pertinent findings. Both lungs were voluminous, particularly in the lower portions. Severe fibrosis and tuberculous nodulation surrounded by emphysematous areas was noted in both apices. The lower lobe of the left lung contained 2 very large air containing bullae measuring 15 cm. in diameter. The right lung, in the antero-basal portion, also contained one large bulla. These bullae greatly compressed the surrounding lung tissue. The bronchi were lined by hyperemic mucosa and the lumina were completely occluded by very thick tenacious mucosa.

The heart weighed 450 grams and the thickness of the right ventricle was 4 mm. and of the left 16 mm. The coronary arteries were normal.

Microscopic Examination.—Examination revealed no apparent increase in the musculature of the bronchi. There was slight thickening of the basement membrane of the bronchial epithelium and there was slight lymphocytic infiltration beneath the basement membrane and in the mucus glands. Cause of death was acute obstructive emphysema, secondary to obstruction of the bronchi by thick mucus, with acute pulmonary emphysema in both lower lobes. Chronic fibroid tuberculosis was present in both apices and there was some cardiac hypertrophy.

CASE 5.—M. W. The patient was a 54-year-old Negro man, who had had asthma since the age of 46. When first examined on August 2, 1949, the essential positive physical findings comprised a rather marked degree of emphysema with wheezing and sonorous râles in both lung fields. There had been numerous hospitalizations since 1948 for control of asthma. Examination of the heart was within normal limits. Electrocardiogram was normal. The chest x-ray showed pulmonary fibrosis and emphysema. Serology revealed a four plus Wassermann. The patient had received treatment for syphilis 20 years previously and had recently completed a course of 10 million units of penicillin.

The patient was placed on the management described below, consisting of spaced dosage of aminophylline, ephedrine, and iodides, but required supplementary injections of adrenalin and occasional intravenous injections of aminophylline. There were four admissions to the hospital before the final admission on August 3, 1951. In September of 1950 treatment with adrenocorticotrophic hormone was required to relieve status asthmaticus. His response to the hormone treatment was good and subsequently he reacted well to the usual antiasthmatic medication. During the final hospitalization the patient was maintained on spaced dosage of broncho-dilators and iodides and appeared to be doing fairly well although he did require supplementary injections of adrenalin. The patient died suddenly on Sept. 15, 1951.

Post Mortem Examination.—Examination showed an acute obstructive emphysema with blockage of the bronchial tree by mucus plugs. The bronchial musculature was markedly hypertrophied, there was evidence of hyperactivity of the mucus glands of the bronchi, and interstitial infiltration of the bronchial glands by lymphocytes and eosinophils.

DISCUSSION

The cases reported here would seem to bear out the concept that intrinsic asthma is a disease of considerable severity which is a definite threat to life, thus differing from the common allergic asthma. The cases detailed in this report fulfill the requirements for asthmatic death in that all died during asthmatic paroxysms. Post mortem examination in each case revealed the typical pulmonary findings of chronic asthma with hyalinization of the basement membrane, hypertrophy of the bronchial musculature, hyperactivity of the bronchial mucus glands and plugs of thick mucus in the bronchi. There was no extrapulmonary cause of death found at post mortem. Each of these cases showed a moderate to marked emphysema.

Case 1 developed asthma at the age of 56, the disease having been present for 6 years before death. Allergy to aspirin was present in this case but the patient received no aspirin or aspirin compounds while in the hospital. He received oral medication of broncho-dilators and potassium iodide in relatively small dosage, but dosage was not spaced throughout the day. Although he was not completely free of asthma during hospitalization he could not be regarded as clinically in status asthmaticus prior to death inasmuch as he had asthmatic attacks only at night and in the early morning.

Case 2 had a spontaneous left pneumothorax but it was felt that this alone would not have caused death in the absence of mucus plugging of the bronchi. This patient was also not in status asthmaticus prior to death. He received spaced dosage of broncho-dilators and potassium iodide while in the hospital, broncho-dilating drugs being given at 6:00 A.M., noon, 4:00 P.M., 8:00 P.M., and 11:30 P.M., and the potassium iodide being given in dosage of 1 Gm. 3 times a day. It is not definitely known whether the patient continued this schedule as he was advised to do during the trial of therapeutic leave. This patient had had asthma for 31 years (since the age of 22) and had a definite allergic history. He represents the group of cases in which intrinsic asthma develops with a background of typical allergic asthma.

Case 3 had a 15-year history of asthma with development of the disease at the age of 38. Clinically this patient represents a typical status asthmaticus with continuous wheezing and dyspnea unrelieved by the medication given. This patient did not receive potassium iodide, nor did he receive spaced dosage of broncho-dilators.

Case 4 had asthma for 7 years with onset at the age of 44. He also had a complicating tuberculosis. Prior to death this patient had an episode of congestive failure which responded to the usual therapeutic measures. He was receiving broncho-dilators (aminophylline and ephedrine 4 times a day, and 0.6 Gm. of potassium iodide 3 times a day). The patient was not in status asthmaticus prior to death and at the time seemed to be making a satisfactory recovery from his cardiac failure with his asthma fairly well controlled.

Case 5 exemplifies the same clinical picture and pathological findings as have described in the previous four patients—there is the onset of asthma late in life, the presence of severe pulmonary emphysema, and death in an asthmatic paroxysm within a few years from the first diagnosis of asthma.

None of these patients received morphine, atropine, or barbiturates, all of which drugs have been frequently incriminated in deaths occurring during asthmatic attacks.

The pathological findings in these cases are those described as typical in bronchial asthma with death due to acute obstruction of the bronchial tree by mucus plugs. The clinical history and physical findings correspond to those of bronchial asthma, with periods of paroxysmal wheezing, respiratory distress, relieved by adrenalin, ephedrine, aminophylline, and iodides. Only one of the five cases, however, had a true allergic asthma at onset. Onset of asthma in the other 4 cases was at ages 38, 44, 46, and 55. The relationship between

allergic or extrinsic asthma and intrinsic asthma is not clear but the finding of identical pathologic findings in the two, and the development of intrinsic asthma in patients who initially show allergic asthma would speak for a close relationship. Rackemann[3] believes that in the younger patients with extrinsic asthma, symptoms depend mainly on bronchospasm due to spasm and edema, relieved by adrenalin. As the asthma persists the element of bronchial exudate enters and this exudate may be altered by an unknown mechanism so as to become extremely viscid, thick and tenacious. The combination of this tenacious mucus and loss of normal ciliary motion may combine to suffocate the patient.

Only one of the patients, Case 3, was in status asthmaticus prior to death. On analysis of these cases it was to be noted that all of these patients had emphysema, that death in each case occurred acutely, and that post mortem examination showed plugging of the bronchial tree with tenacious mucus. It was felt that continued spaced dosage of bronchodilators and an adequate dosage of potassium iodide should give protection against an acute obstructive episode such as caused the death of these patients. Review of the medication in 3 of the patients (Cases 1, 3, and 4) reveals that the broncho-dilating medication was not given in spaced dosage, and the potassium iodide dosage was rather low in 2 cases and no potassium iodide was given in Case 3. In Case 2 the patient did very well on spaced dosage but it is not known whether the spaced dosage was continued after the patient left the hospital for the 3 weeks prior to his death. Case 5 represents failure of control of the respiratory difficulty by spaced dosage of broncho-dilators and iodides. Although the patient was taking his medication faithfully and to the limit of his tolerance, the bronchial secretions became viscid and profuse enough to block the bronchial tree.

In the past 2 years it has been our policy in patients in the older age group, who have considerable pulmonary fibrosis and emphysema and asthma, to use broncho-dilator drugs in spaced dosage around the clock to afford protection throughout the 24 hours. The broncho-dilating drugs employed have been aminophylline and ephedrine, and the individual dosage is adjusted to the patient's need and tolerance for the drug. The dosage of aminophylline has averaged 0.27 Gm., and of ephedrine, 25 to 50 mg., usually given at 6:00 A.M., noon, 4:00 P.M., 8:00 P.M., and midnight.* Potassium iodide is given in sufficient dosage 2 or 3 times during the day to insure a liquid sputum. Adrenalin is infrequently required on such a regimen. In patients with acute asthmatic paroxysms, in addition to intravenous aminophylline, intravenous sodium iodide has been found of considerable value in liquifying the sputum and affording bronchial drainage. Our patient population, as noted above, includes a large percentage of patients who had been sent to this part of the country because of severe intractable pulmonary disease. The above regimen of treatment has been found quite efficacious, as during the past 2 years only one of our patients (Case 5) has died in an asthmatic paroxysm. In the event of a severe attack of bronchial obstruction not responding to other measures,

*This form of therapy was suggested by Seymour Robins, M.D., of our medical staff, who learned it from Joseph Boch, M.D., of Patchogue, New York.

tracheal suction should be employed. The terminal episode in the cases described was of such rapidity as to preclude bronchoscopy, but the passage of a tracheal catheter with suction, or even tracheotomy with suction through the tube, might be worth trying in such a case. The pathological findings of widely distributed thick mucus plugs which are tenaciously adherent in all of the small bronchi would indicate that such treatment would be unlikely to succeed.

CONCLUSIONS

1. A series of five patients dying in asthmatic paroxysm is presented, with consideration of the therapeutic implications and description of post mortem findings.

2. The mechanism of death in asthmatic paroxysm is discussed.

3. A schedule of treatment for patients in the older age group with severe intrinsic asthma is described.

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A CLINICAL REPORT ON THE TREATMENT OF CONTACT DERMATITIS WITH ADRENOCORTICOTROPIC HORMONE IN OIL

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ADRENOCORTICOTROPIC hormone, ACTH, in aqueous solution, has been administered to patients suffering with exfoliative dermatitis from the ingestion of drugs or the injection of penicillin. Reports of improvement following aqueous ACTH therapy of patients suffering with industrial dermatoses have also appeared in the literature.[1] The therapeutic results obtained have been gratifyingly beneficial. However, patients have had to receive injections every four to six hours and hospitalization has been necessary. This method of treatment is both an economic hardship and an administrative burden. The following data report the benefit which ambulatory patients suffering with an acute contact dermatitis of known etiology have derived by the administration of ACTH suspended in oil.

CLASSIFICATION OF PATIENTS

The patients in this report divide into two groups: (a) those who developed extensive dermatitis after the application of medicated ointments or cosmetics (b) those who developed violent dermatitis after contact with Rhus toxicodendron (poison ivy). No known intrinsic factors entered into the cause of the dermatitis.

METHOD OF TREATMENT

Before the treatment began, each patient was examined; blood morphology, serology, and chemistry were recorded. In each case the findings were within the range of normal. Blood pressure readings were normal in 7 patients, high in 1 patient.

The injections, administered daily, were made in the buttocks. The amount of ACTH varied, for the age of the patient and the condition of the patient's skin after each injection determined the next dose.

CASE REPORTS

CASE 1.—S., a 77-year-old woman, developed an ulcer on her leg about two years previously. Under local treatment (elsewhere) the ulcer improved, but eight months before being seen at the Clinic it broke down because of impaired circulation. For six months she used various ointments with no improvement. Two months prior to consultation at the Clinic, Thephorin ointment was prescribed. Coincidentally with its application to the ulcer, an eruption developed, not only on the ulcerated leg but also on the opposite leg, and gradually spread over the entire body. Unfortunately she continued the direct application of this new ointment until she came to the Clinic.

From the Allergy Clinic of the Medical Department of the Johns Hopkins University and Hospital.

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The eruption was characterized by red macular, itching lesions with marked edema of the legs from the hips to the ankles. Immediately all local treatment was discontinued, and the patient was given 100 mg. ACTH in oil. On the second day the skin showed remarkable improvement and the edema had diminished. She was given 160 mg. of ACTH. The improvement on the third day was even more striking than that on the second day had been. She was given an additional 160 mg. of ACTH. In 48 hours she again reported for observation. The eruption had cleared from her body, the edema had entirely subsided, and the area of inflammation about the ulcer had diminished. No further ACTH was required. The total dosage was 420 mg.

Subsequently a patch test with Thephorin ointment, the offending medication, gave a marked reaction. The eosinophil count before treatment was 1456 cells per cubic millimeter. The eosinophil count after treatment on the third day was 88 cells.

CASE 2.—T., a 41-year-old man, had had recurring eruptions on his face since he first began to shave at the age of 16. Later, when an electric razor was used, the irritation was lessened. However, since January of 1951, he has complained of "welts" appearing on his face and clearing only after extensive desquamation. In spite of various medications, these eruptions recurred persistently until he became incapacitated because of great swelling of the eyelids, mouth, ears, neck, and shoulder girdle.

A review of his history revealed that he frequently washed his thick hair with various commercial preparations, most often with Fitch Shampoo.

Examination.—At the time of his consultation there was marked swelling of the face, especially the eyes and ears. The face was fissured and serum was being exuded. The skin of the neck and shoulders was intensely red and swollen.

Treatment.—On the first day 120 mg. of ACTH in oil was given intramuscularly. Within 24 hours a remarkable improvement occurred. The swelling completely subsided; the itching became less disturbing; the redness over the shoulders diminished. On the second day 100 mg. of ACTH in oil was administered, on the three following days 80 mg., 40 mg., and 40 mg., respectively, were given. The total dosage was 380 mg. The eosinophil count before treatment was 354 cells per cubic millimeter. The count dropped rapidly on the subsequent days to 22 cells, 40 cells, 11 cells, and, on the last day of treatment, was 176 cells. The skin cleared, then normal color and texture rapidly appeared. Subsequently, a patch test of Fitch Shampoo was violently positive after 24 hours.

CASE 3.—M., a 60-year-old man, had complained of itching around the rectum for three years. With various treatments, remissions had occurred, but in October of 1950, the irritation spread from the rectum over the buttocks. The skin cracked, burned, and there was considerable exudation.

Examination.—The skin around the rectum and over the buttocks was intensely inflamed. There was much exudation, and the patient complained of great pain due to the fissures.

Treatment.—On the first day 60 mg. of ACTH in oil was given intramuscularly. Within two hours there was relief of itching and burning, and by the next day the acute inflammation had subsided. On the second day 60 mg. of ACTH in oil was administered. The total dosage was 120 mg. Additional treatment was considered unnecessary because of the rapid improvement, and subsequently the condition of the skin became soft and free from irritation. The eosinophil count before treatment was 913 cells per cubic millimeter. After the first treatment, the count rose to 957 cells. A patch test of Nupercainal ointment, which the patient had formerly used repeatedly about the rectum, was violently positive after 12 hours.

CASE 4.—Sister G., a 56-year-old woman, had suffered with a vascular problem of 20 years' duration, a phlebitis having developed after a pelvic operation. In January of 1950, a dermatitis so severe that hospitalization was necessary developed over both lower extremities because of impaired circulation. X-ray therapy improved the condition temporarily, but in January of 1951, ligation of the veins of the left leg was performed

because of a recurring phlebitis, and subsequently a double sympathectomy became necessary. There was temporaary improvement of the skin; however, redness and itching soon recurred, ointments were again applied, and the skin rapidly became worse.

Examination.—An extensive dermatitis involved both lower extremities from ankles to knees. The skin was red, there was a serous exudate, with intense itching and desquamation.

Treatment.—On the first day 80 mg. of ACTH in oil was given intramuscularly, and on the two following days 60 mg. and 40 mg., respectively. There was no appreciable change in the condition of the skin, for the patient had continued to apply the offending ointment, Stearin-Lanoline. This application was stopped. On the fourth day, she was given 40 mg. of ACTH in oil, likewise, on the fifth day. The improvement was remarkable. Redness, exudation, and desquamation rapidly cleared, and after the sixth dose of ACTH in oil (40 mg.) the patient's condition was excellent. The total dosage was 300 mg. The eosinophil count before treatment was 143 cells per cubic millimeter. Subsequently it dropped to 88 cells, but after the sixth treatment the count was 132 cells. A patch test with the ointment Stearin-Lanoline was violently positive after 24 hours.

CASE 5.—E., an 11-year-old girl, had been exposed to poison ivy 24 hours before an eruption appeared on her face, neck, arms, body, and legs. She had had similar eruptions in each of the five preceding years. Previously a patch test had been violently positive after 24 hours.

Examination.—There was an extensive red vesicular eruption over the face, neck, trunk, arms, and legs; the eyelids were swollen; itching was general and intense.

Treatment.—On the day of examination she was given 60 mg. ACTH in oil intramuscularly. On the second day the eruption was worse; the eyelids were swollen shut; sedation during the previous night had given no relief. Eighty milligrams of ACTH in oil was now given. On the third day the patient's skin showed great improvement; blanched areas of normal skin had developed on the cheeks and around the mouth and eyes; itching had subsided and the edema had become less. On the third day 60 mg. of ACTH in oil were given. The total dosage was 200 mg. On the fourth day the child, free of discomfort, returned to school. The eosinophil count before treatment was 200 cells per cubic millimeter. There was no change in the count after the second treatment.

CASE 6.—P., a 26-year-old man, had been exposed to poison ivy forty-eight hours before the eruption developed.

Examination.—There was an extensive dermatitis of the face, hands, arms, and legs. Since early childhood he had had numerous similar reactions from contact with poison ivy. On previous examination, a patch test of Rhus toxicodendron had been violently positive after 48 hours.

Treatment.—On the day of examination he was given 40 mg. of ACTH in oil intramuscularly. By the second day the eruption had spread; the itching was intense; the face had become extremely swollen. He was given 60 mg. of ACTH in oil intramuscularly. When he reported on the third day, great improvement was noted. The swelling, redness, and itching had subsided and, unlike previous reactions from poison ivy contact, no vesiculation occurred. He was given 25 mg. ACTH in oil. His subsequent course was characterized by rapid improvement, and no further treatment was necessary. The total dose of ACTH in oil was 125 mg. The eosinophil count before treatment was 0. After the second treatment, the count was 66 cells.

CASE 7.—W., a 48-year-old woman, had been exposed to poison ivy four days before she developed a dermatitis involving the face, arms, and legs. She gave a history of having eruptions whenever she came in contact with Rhus toxicodendron.

Examination.—A vesiculating eruption covered the cheeks, forehead and eyelids. A macular erythema spread over the neck; the forearms and legs showed a similar eruption.

Treatment.—On the day of examination the patient was given 40 mg. of ACTH in oil intramuscularly. By the second day the eruption on the face had cleared; the vesicles

TABLE I. CONTACT DERMATITIS FROM MEDICATION

CASE	NAME	AGE (YRS.)	DERMATITIS		ACTH IN OIL		EOSINOPHILS—CELLS PER CUBIC MILLIMETER		CLINICAL RESULT
			CAUSE	DURATION	DOSAGE (MG.)				
1.	S.	77	Thephorin ointment*	8 mos.	1st day	100	Before treatment	1456	Greatly improved in 24 hours. Recovery complete in 3 days.
					2nd day	160			
					3rd day	160		88	
					Total	420			
2.	T.	41	Fitch shampoo†	4 mos.	1st day	120	Before treatment	354	Greatly improved in 24 hours. Recovery complete in 6 days.
					2nd day	100		22	
					3rd day	80		44	
					4th day	40		11	
					5th day	40		176	
					Total	380			
3.	M.	60	Nupercainal ointment‡	6 mos.	1st day	60	Before treatment	913	Greatly improved in 24 hours. Recovery complete in 3 days.
					2nd day	60		957	
					Total	120			
4.	G.	56	Stearin-Lanoline ointment§	6 mos.	1st day	80	Before treatment	143	Greatly improved in 24 hours, after omitting ointment on 3rd day. Recovery complete in 3 days.
					2nd day	60		77	
					3rd day	40		88	
					4th day	40		88	
					5th day	40		121	
					6th day	40		132	
					Total	300			

*Contains Thephorin (phenindamine) in a carbowax base.

†Contains quinine, potassium bicarbonate, methyl salicylate, potassium acetate, oil lavender, and saponified cocoanut oil.

‡Contains 1 per cent Dibucaine (a-butyloxycinchonic acid diethylethyenediamide).

§Contains stearic acid, anhydrous lanolin, white bees wax, cetyl alcohol, sesame oil, liquid petrolatum, butyl parahydroxy benzoate, triethanolamine, powdered borax, distilled water, carbitol, and oil of rose.

TABLE II. RHUS TOXICODENDRON DERMATITIS (POISON IVY)

CASE	NAME	AGE (YRS.)	FREQUENCY	SEVERITY OF REACTION	DOSAGE ACTH IN OIL (MG.)		EOSINOPHIL RESPONSE		CLINICAL RESULT
							Before Rx	220	
5.	E.	11	Every year for five years.	Violent	1st day	60			
					2nd day	80		220	Greatly improved in 2 days. Complete recovery in 4 days.
					3rd day	60			
					Total	200			
							Before Rx	0	
6.	P.	24	Every year since childhood.	Violent	1st day	40			
					2nd day	60		66	Greatly improved in 3 days. Complete recovery in 5 days.
					3rd day	25			
					Total	125			
							Before Rx	165	
7.	W.	48	Every year since childhood.	Violent	1st day	40			Greatly improved in 24 hours. Complete recovery in 2 days.
					2nd day	20		110	
					Total	60			
							Before Rx	0	
8.	C.	50	Recurring episodes of dermatitis	Violent	1st day	60			
					2nd day	60		11	Greatly improved in 3 days. Complete recovery in 5 days.
					3rd day	40		11	
					Total	160			

were dry; and the swelling of the tissue had subsided and the redness had lessened. The skin of the arms and legs had lost the redness, and itching had ceased. She was given 20 mg. of ACTH in oil. On the third day the eruption subsided to such an extent that no additional therapy was required. The total dose of ACTH in oil was 60 mg. The eosinophils before treatment numbered 165 cells per cubic millimeter; on the second day they numbered 110 cells.

A patch test of Rhus toxicodendron was violently positive after 72 hours.

CASE 8.—C., a 50-year-old woman, was the wife of a florist. Her contacts with plant life have been multiple. As a child she developed dermatitis from the pollen of ragweed and the juice of tomato plants. Subsequently she developed eruptions in any season of the year from greenhouse plant contacts such as sweet peas, carnations, iris, and from insecticides. Patch tests with these flowers and the several insecticides were positive after 48 hours. Patch tests with Rhus toxicodendron and ragweed pollen were negative.

Examination.—A diffuse papular eruption spread over the face, neck, and arms.

Treatment.—On the first day the patient was given 60 mg. of ACTH in oil intramuscularly; on two subsequent days she was given 60 mg. and 40 mg., respectively. A total of 160 mg. was administered. Improvement in this patient was slower than that in the patients with poison ivy dermatitis. However, on the fourth day the skin was so much better that further treatment with ACTH was discontinued. The eosinophil count before treatment was 0. After the second and third injections, the eosinophil count was 11 cells.

DISCUSSION

Three patients had repeatedly applied medicated ointment to affected areas; two of them to leg ulcers, and the third patient to an irritated rectum. The medication had been continued for a number of weeks although violent and extensive dermatitis due to unsuspected sensitivity had ensued—not only at the sites of application but in widely removed areas as a result of contact on the normal skin. The fourth patient for a number of months had used a commercial hair shampoo. Sensitivity which developed was not recognized, consequently violent inflammation occurred after each application.

Four other patients were treated with ACTH in oil for an acute dermatitis following contact with Rhus toxicodendron (poison ivy) and other plant juices. Prophylactic desensitization by injection of extracts of specific plant antigens has been successful in a large number of sensitive patients, but the treatment with antigens has been disappointing and of questionable value once severe dermatitis has developed.

Three of the eight patients treated with ACTH in oil gave histories of annual poison ivy contacts and consequent violent dermatitis. A fourth patient, the wife of a florist, gave a history of sensitivity to the juice of many plants. Local treatment to the skin had become of no value in her case.

In these patients recovery from previous cases of dermatitis had been very slow, from two to four weeks after the onset of symptoms. In the same patients, ACTH in oil improved the skin in each case on either the second or the third day. No other remedy has been comparable to this drug.

Untoward reactions from the administration of ACTH, aqueous and in oil, have been reported. Selection of patients should be based on the criteria that have been published in previous reports. Several of these patients complained

of local swelling, redness, and fever at the site of injections, the buttocks. These reactions appeared either three or four days after the last injection, and subsided within 72 hours without other sequelae.

SUMMARY

The administration in a single daily dose of this slowly absorbed preparation has great advantage over the schedule of multiple dosage required by the aqueous ACTH solution. The economy to the patient, the convenience to the physician, the gratifying results obtained clinically by the patient, all warrant continued use of ACTH in oil—whether the eruption is the result of medication locally applied or of contact with plant life. The amount of ACTH required to relieve contact dermatitis averaged 220 mg. administered in from two to six doses, one injection daily.

Since the completion of this study, the authors have had the opportunity to use adrenocorticotropic hormone in gelatin. The results of treatment have been equally as satisfactory as those obtained with the hormone in oil.

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TREATMENT WITH ACTH AND CORTISONE OF ATOPIC DERMATITIS (ECZEMA) IN INFANTS AND CHILDREN

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IT IS an interesting commentary on the present-day methods of the management of atopic dermatitis (eczema) in pediatric practice that since we treated our first case with ACTH in May of 1950 in the months elapsing since, in a practice largely devoted to pediatric allergy, we have encountered but four additional cases in which we have felt that hormone therapy was indicated. A preliminary report has been made upon three of these five patients.[1] It is the purpose of this communication to report the further progress of these cases and to add two additional. Besides our preliminary report, there are few others in the literature. Kanee et al.[2] reported one case treated with ACTH and Randolph and Rollins[3] and DiGeorge and Nelson[4] three cases each. These authors had little to say beyond the fact that their cases cleared rapidly without complications and recurred when the therapy was discontinued.

Cooke and associates[5] discussed five children, sex not stated, with generalized allergic dermatitis (eczema). One infant 7 months old was treated with cortisone and four others ranging in age from 1½ to 2½ years were treated with ACTH. All responded well with relief varying from 5 to 50 days after cessation of therapy. None were carried along on maintenance doses. It was observed that in infants and children the skin became quite normal save for pigmentation which cleared quite slowly. In older patients with longer duration of the disease tissue changes with lichenification remained and no patient was under continuation therapy long enough to observe resolution of what was regarded as permanent skin induration.

An incidental observation was to the effect that the gamma globulin values of 4 children suffering from infantile eczema were significantly elevated. There was also elevated alpha globulin and normal beta globulin, with distinctly decreased albumin values. Accordingly the albumin-globulin ratios were noticeably lower in these sera. This differs from the findings of Wolpe[6] who reported that the globulin fraction tended to show a greater deviation below normal than the albumin. Cooke and associates state that in their cases the rather high incidence of elevated alpha globulin in infantile eczema recalls a report of Shedlovsky and Scudder[7] who attributed increased alpha globulin levels of human sera to any considerable inflammation or tissue destruction, regardless of its causes.

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Our procedure in the routine management of infantile eczema is still essentially as has been previously described.[8] This consists of a very detailed history; a complete physical examination; complete skin testing, using passive transfer tests if the skin cannot be tested directly; environmental control; local treatment; hospitalization and other management as indicated by the results of the study as a whole. The cases here reported failed to respond to a thorough trial of these measures and it was felt that they were of sufficient urgency to indicate hormone therapy. The methods for the control of this type of therapy have been previously reported.[1] The details of our cases are in summary as follows:

CASE REPORTS

CASE 1. (8767)—This was a boy first seen at the age of 3 months who had had severe eczema since the age of 3 weeks. This presented the typical picture of atopic erythroderma. He was intensively studied and treated with varying and inconstant results until, at the age of 15 months, it was felt that his condition was serious. No progress was being made and the family was in despair. He was hospitalized for ACTH therapy and started on a dose of 2.5 mg. every 6 hours by intramuscular injection. After 48 hours, since no improvement had occurred, the individual doses were increased to 8 mg. following which his skin steadily improved. He was discharged after 11 days of hospitalization, having received a total of 175.9 mg. of ACTH. He had lost 120 Gm. (4 oz.) during that period and his skin was almost clear.

Following discharge the skin gradually became worse necessitating readmission to the hospital at the age of 17 months. The skin did not improve. ACTH (10 mg.) every 6 hours was started. In two days the skin had cleared remarkably and in three days was almost clear. He was discharged on the twenty-sixth hospital day. He had gained 300 Gm. (10 oz.) in weight and had received a total of 270 mg. of ACTH. The dose of 10 mg. every 6 hours was continued at home and, after a week the skin remaining clear, the dosage was reduced to 10 mg. every 8 hours. On this dose the skin again became somewhat worse but it was decided to discontinue the medication. While on the drug it was noted that the boy was distinctly euphoric. In the two weeks at home he had received a total of 470 mg. of ACTH. Six weeks later, at the age of 20 months, his skin was again severely eczematous. He began getting occasional mild asthmatic attacks and his skin gradually cleared, possibly associated with the change in shock organ. Direct skin testing was done. Many positive reactions were obtained and these corroborated in every instance the results previously obtained by passive transfer tests. Under the usual methods of treatment the dermatitis and the asthma both came under good control. He was last seen at the age of 2 years and 8 months. He was still on a limited diet, omitting egg, milk, beef, tomato and citrus fruits but weighed 16 kg. (35 lbs.), was well developed and nourished with a skin that was so nearly normal that smallpox vaccination was seriously considered. However, since he still had some itching it was decided to defer this.

CASE 2. (9489)—This girl was first seen at the age of 23 months because of generalized eczema which had started at the age of 5 weeks. She had also had an occasional attack of bronchial asthma since the age of 18 months. She further suffered from congenital heart disease, probably a minimal pulmonary stenosis, which produced no symptoms other than the murmur. The usual methods of treatment for eczema did not help and at the age of two years she was hospitalized with only minimal improvement resulting from the change in environment during an 8 day period. She was then started on 8 mg. of ACTH every 6 hours. Within 2 days the skin started to clear remarkably and this continued to such an extent that at the end of a week, direct skin testing could be done. These tests corroborated results previously obtained by passive transfer tests. On the thirteenth hospital day, on a routine determination, her blood pressure was found to be 130/80. The ACTH was reduced to 2.5 mg. every 6 hours. The blood pressure rapidly returned to normal and hypertension did not

recur. On the sixteenth hospital day, while still on ACTH and with a progressively clearing skin, she had a moderately severe asthmatic attack of short duration, the cause of which could not be determined. She was discharged on the eighteenth hospital day with the skin almost clear. A total of 200 mg. of ACTH had been administered over a period of 9 days. The skin remained clear for a period of 11 days and then became progressively worse and 22 days after discharge appeared almost as bad as when first seen. Hospitalization was again advised but refused by the mother because she felt that the child was better, particularly since the itching seemed much less severe than previously. Under pediatric-allergic management the child steadily improved. When last seen at the age of 3 years she had had no asthma for well over a year. Her skin was relatively clear though generally rather dry and she had a few small patches of chronic atopic dermatitis on her calves.

CASE 3. (10120)—This was a deaf mute, 14 years of age, who had had severe, generalized chronic atopic dermatitis since early childhood. She had been thoroughly studied for years without relief in various clinics. As she progressed into adolescence she developed marked mental depression and became a psychiatric problem. Although such conditions are considered as contraindications to the use of hormone therapy of this type, it was confidently felt that her mental depression was due to the disfigurement caused by the eczema. She was hospitalized and cortisone therapy instituted because she did not give a good response to the Thorn eosinophil depression test. Over a 29-day period she received 4050 mg. by intramuscular injection. She made a striking recovery, mentally and physically. She was discharged, but 3 weeks later her condition had reverted to the same state as before hospitalization. She was again hospitalized and this time cleared well over a period of 21 days, during which she received 1060 mg. of cortisone by injection and 800 mg. by mouth. She was continued at home on oral cortisone, meantime coming into the office for direct skin testing. All tests were negative. The oral cortisone at home was then discontinued and within 2 weeks her skin and mental condition again became very much worse. She was then put on a very strict elimination diet. The first week she showed no improvement whatsoever, but since then her skin has steadily improved. New foods have been gradually added to her diet and she is now apparently able to tolerate all but eggs, chocolate, tomatoes and citrus fruits. Her skin, terribly indurated and pigmented from many years of dermatitis, is gradually becoming clearer and softer. She itches only at night and this can be controlled by Benadryl. Her improvement can be best summarized by the words of the nurse at the Rochester School for the Deaf who brings her to the office: "We used to see her almost every day. She always had something to complain about and would cry from itching. Now we hardly ever see her except at night when she comes for Benadryl. She is not mentally depressed and she plays with the other children, which she never did before."

CASE 4. (9817)—This was a 6-month-old girl who was referred because of eczema since the age of 6 weeks. She had been treated by very capable pediatricians without relief, and our studies contributed nothing helpful. After 9 months of such experimentation she was hospitalized for ACTH therapy, and after a control period of a week, during which she did not improve, she was started on 5 mg. of ACTH every 8 hours over a period of one week, during which she received 85 mg. Her skin improved about 90 per cent. Since discharge, a period of over 6 months, her skin has steadily improved under the usual methods of treatment.

CASE 5. (9299)—This boy was first seen at the age of 1½ years. He had had chronic atopic dermatitis since the age of 6 weeks. It was distributed in the areas usual at this age (the folds of the elbows, knees and neck and about the wrists and ankles). There was also some on the face and on the backs of the elbows. The chief complaint was pruritus and he was practically never free from some local secondary infection due to scratching. Exhaustive studies and treatment gave no relief after a 2 month period, so the usual blood chemical and other studies preliminary to ACTH therapy were carried out and it was decided to treat him on an ambulatory basis. He was started on 10 mg. of ACTH intramuscularly every 6 hours at home, and after 5 days definite improvement in the skin was noted. His appetite also im-

proved and during a 5-day period he gained 575 Gm. (1 lb., 2 oz.). This gain did not appear to be due to edema. The ACTH was continued for 6 more days with remarkable improvement as regards the clearing of the skin and itching. The dose was then reduced to 10 mg. every 8 hours. On this dose, however, he failed to improve and a reducing substance (1+) was noted in the urine. One week later, while on the same dose of ACTH, the urine showed no reducing substance but did show albumin, one plus. Meantime, his weight and blood pressure had remained unchanged and he had more itching and more rash. This continued for another week when it was observed that his eyes became puffy and the albuminuria increased to three plus. It was therefore decided to discontinue the ACTH.

Further studies indicated that the child had developed a typical mild nephrosis while on ACTH therapy. This has now persisted over a 6 month period, but the symptoms are minimal and the albuminuria is gradually decreasing. The local skin condition is fairly well controlled by symptomatic therapy. Since ACTH has proved a potent agent for the treatment of edema due to nephrosis[9] it is at least suggested by this case that ACTH has no influence on the etiological factors which govern the development of nephrosis.

CORTISONE OINTMENT

The experiments of Bordley,[10, 11] who showed reduction of nasal manifestations of allergy, as polyps and congested turbinates following the administration of a nasal spray containing 8 mg. of cortisone per c.c., suggested that cortisone ointment might be used locally in the treatment of atopic dermatitis. Cortisone* was shown not to be inacitvated by incorporation with ointment base. In 20 cases of atopic dermatitis we were unable to show that the cortisone ointment helped any more than a control ointment. At the meeting of the Section on Pediatrics of the A. M. A. this past summer, a distinguished investigator showed Kodachrome slides of an infant who showed remarkable improvement following the use of cortisone ointment, but he did not state whether or not a control ointment had been used. Levin and Moss[12] reported on 15 cases treated with cortisone ointment with apparent benefit in 2 cases, but they also did not mention the use of a control ointment. They quote Haley to the effect that he also found cortisone ointment ineffective in a number of cases of eczema.

DISCUSSION

Baer and Leider[13] have recently reviewed the literature concerning the use of ACTH and cortisone in allergic skin diseases. They emphasize the fact that, as in all other diseases treated with these drugs, they do not produce cures. However, these hormonal agents, while they are being administered, exert dramatic effects in some cases of allergic dermatoses. There is usually a return of the symptoms and signs of the disease within a more or less short period of time after cessation of therapy unless: (1) the allergic reaction has run its full course during the period while the patient was under treatment, or (2) it has been possible to find and eliminate the allergic agent during the period while the patient was under treatment.

Baer and Leider further state that the indications for the use of ACTH and cortisone in atopic dermatitis are: (1) to control severe exacerbations of a relatively otherwise stationary eruption, and (2) to permit orthodox forms of

*Cortisone ointment, 2.5 per cent, supplied by Merck and Co.

therapy to become more effective. This refers to those severe cases of atopic dermatitis in which the patient cannot obtain relief from any of the accepted forms of therapy, i.e., while the patient is in a state which is in some ways similar to status asthmaticus. When ACTH or cortisone is administered in such cases, even if these agents do not completely control the eruption and itching, some patients again respond to topical medication and systemic antipruritic therapy. (3) While ACTH and cortisone should not as a rule be used in atopic dermatitis over long periods of time, there are some otherwise intractable cases in which very small maintenance doses (e.g., cortisone 25 mg. daily) are adequate to keep away the eruption and itching. In such exceptional cases it seems warranted to continue the medication over protracted periods of time.

As far as children are concerned, I am in agreement with Baer and Leider, although as yet we have carried along no eczematous children on small maintenance doses for any significant period of time. I have done this, however, in the case of asthmatic children. To the conclusions of Baer and Leider, I should like to add that these agents may be used to clear the eczematous skin at least temporarily, so that direct skin tests may be done instead of having to resort to passive transfer testing. In such instances we have found that direct skin testing invariably corroborates the results of passive transfer testing.

Lever,[14] recently reviewing the Boston experience, stated that in atopic dermatitis the response is good, but from the limited experience gained so far it seems that in atopic dermatitis the rebound of the disease, after discontinuing the therapy, is worse than in most other diseases. As far as my personal experience is concerned, rebound exacerbation of the eczema did not occur.

Lever also mentioned a 1-year-old child with atopic erythroderma whose response to treatment was excellent, but who relapsed on discontinuance of the therapy, developed pneumonia and otitis media, and died. I would not, however, feel that this death should be attributed to the use of hormone therapy. It is now well known that these drugs mask the symptoms of infection so that death may even occur from pneumonia, for example, before the patient or the physician suspects the presence of a complicating disease. Anyone under treatment with these drugs must be most carefully watched for the development of intercurrent infections and treatment vigorously instituted if there is any question at all about their presence.

SUMMARY AND CONCLUSIONS

It is difficult to draw conclusions from such a limited series of patients as here presented. However, it is suggested, in the light of our experience, that infants and children, with their great natural recuperative powers, while in the process of getting relief from hormone therapy have a much greater tendency to ultimate recovery than is the case with adults. This would be particularly true if, while under treatment with hormones, the children are properly managed by the methods at present in use by pediatric allergists.

The following summarizes our experience:

1. Five infants and children, varying in ages from 6 months to 14 years, were treated with ACTH or cortisone.

2. Good temporary results were obtained in all cases. The restitution of the skin was in no instance completely to normal, but in every instance was satisfactory from the standpoint of itching and of the appearance of the patient.

3. The only complications which appeared in this series were in the case of one child who developed a transient rise in blood pressure which subsided promptly on reducing the dose of ACTH. This same patient, while under treatment with ACTH, developed an attack of asthma, which suggests that it requires a larger dose of ACTH to control asthma than eczema when both occur in the same individual. Another child, while under ACTH therapy, developed mild but typical nephrosis. This suggests that, while ACTH is useful in treating the edema of nephrosis, it has no influence on the etiologic factors in this disease.

4. The presence of a depressive state, when this was due to the presence of atopic dermatitis in an adolescent girl, was not considered a contraindication to the use of hormone therapy, and the depression disappeared on 3 successive occasions as the eczema cleared, the first two times under hormone therapy.

5. Patients under hormone therapy must be most carefully watched for symptoms of infection which may be masked by the use of these drugs.

6. The evidence is that both ACTH and cortisone produce the same therapeutic effects as far as eczema is concerned. Cortisone should be tried first if the result of the Thorn test is negative. We, and apparently others, used ACTH for the reason that this drug was readily available whereas cortisone was not. Eventually, it is my opinion that where long-term therapy is necessary one will alternate between courses of ACTH, which cause hypertrophy of the adrenal gland, and cortisone, which causes atrophy, in an effort to maintain a reasonable balance. Eventually, laboratory tests may be devised to assist in this procedure.

7. ACTH or cortisone therapy should not be employed until all other forms of orthodox therapy have been tried without relief, and these drugs should not be used even then unless the patient is urgently in need of relief. While these drugs are being used, intensive study of the patient as to possible etiological factors should be continued.

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LOCAL SENSITIVITY TO EPINEPHRINE OF ANIMAL ORIGIN

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A SMALL number of cases showing local inflammatory reaction, following the use of epinephrine of animal origin, has been described.[2-4] The following two patients were seen in the Allergy Clinic of the Montreal General Hospital.

CASE REPORTS

CASE 1.—E. D., a 38-year-old white garage man whose asthma began at the age of 24 years. Within one year he was maintained on epinephrine by hypodermic injection. He took between one and two ounces (30 to 60 ml.) of 1-1000 epinephrine per week with an estimated consumption of between 10 and 12 gallons of the material in thirteen years. After an inaccurately remembered period (probably between one and two years), he began to manifest reaction at the site of each subsequent inoculation. Under our observation, and with sterile technique, inflammation developed at an inoculated site within three to six hours. Redness and swelling covering an area of 2 to 3 cm. in diameter, with central necrosis occurred, and healing followed with a depressed cicatrix. This succession of events covered 7 to 10 days. He had been giving his own injections rather superficially because he was sure he obtained relief more quickly in this way than by deeper subcutaneous injection.

Investigation and Observation.—He was afebrile. Blood pressure, 110/65; Hgb, 92 per cent; W.B.C. 10,100, and eosinophils, 12 per cent. The cardiovascular system was not abnormal. The Wassermann test was negative, and x-ray of lungs, negative. As far as could be determined, his asthma was of the intrinsic type, but we were unable to relate it to any ingested material, or to inhalants. His skin on intradermal testing showed slight reaction to cotton seed, banana, spinach, egg white, chocolate, and corn extracts, and moderate reaction to house dust. Attempted housedust hyposensitization was not beneficial, nor was dietary control or change of environment. The symptoms were perennial. Tonsillectomy and extraction of diseased teeth did not relieve his asthma. Psychiatric investigation revealed that there may have been some relationship between his marriage, his foster parents, and his symptoms.

The skin lesions were limited to areas where epinephrine had been injected (Fig. 1) over the upper arms, and the buttocks. Injection of epinephrine 1-1000, of animal origin, intradermally, into any of these areas, in the scar itself, or between scars, produced local inflammation. Deep subcutaneous injection did not produce a recognizable reaction, but this may have been an inaccurate observation as it is difficult to say by palpation in this nodular area if a deeper fresh nodule is present. The possibility of contamination of the syringe or needle by alcohol or any other agent was rigidly excluded and the reactions occurred under bacteriologically sterile technique.

Injection of epinephrine 1-1000 of animal origin in a site not previously used did not result in any local inflammation, nor did previously inflamed sites become reactivated. A remarkable blanching of the skin lasting over twelve hours did occur over an area of 4 cm. in diameter. Injection of synthetic epinephrine in scarred areas did not produce any local reaction; nor did Butanefrin (Winthrop), Isuprel (Winthrop), Neo-Synephrine (Winthrop), Vaponefrin (Vaponefrin Co.), or nor-adrenalin.

The skin did not react to intradermal extracts of pork or beef skeletal muscle, nor did it react to extracts of pork or beef adrenal glands, from which epinephrine was absent.

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This epinephrine did not produce reaction in scarred sites. Pure crystalline epinephrine of animal origin in saline with no buffer, or preservative, in scarred sites produced a typical inflammatory nodule followed by necrosis. Passive transfer tests were negative.

CASE 2.—G. W., a 65-year-old (approximately) white, male, married laborer. The history is very vague due to his unreliable memory. He had had asthma for at least 20 years, perennial, without seasonal exacerbations. His blood pressure was 135/90, and Wassermann negative. An x-ray of the lungs was negative. Hgb. 90 per cent, W.B.C. 8,500, and eosinophils 4 per cent. The cardiovascular system was not abnormal.

Investigation and Observation.—The skin on intradermal testing reacted moderately to cat dander, horse dander, feather, and ragweed extracts, but none of these was opreative etiologically at the time. Cold air was the only factor demonstrably related to his asthma. Intradermal injection of epinephrine 1-1000 of animal origin in scarred sites produced local inflammation followed by necrosis and scarring. Injection of the same material in unscarred (not previously used) areas produced no inflammation. Subcutaneous injections in the old scars led to no reaction. Blanching of the skin was not as extensive or prolonged as in Case 1. Injection subcutaneously or intradermally, of synthetic epinephrine in scarred or unscarred sites produced no inflammation at the site, nor at previously inflamed sites. No inflammatory reaction was obtained to Butanephrine, Isuprel, Neo-Synephrine or Vaponefrin, or nor-adrenalin. Using epinephrine of animal origin, local reaction occurred under bacteriologically sterile technique, and with a chemically clean syringe and needle.

The skin did not react to intradermal extracts of beef or pork skeletal muscle. Extracts of beef and pork adrenal glands, containing no epinephrine, produced no reaction in previously inflamed sites, or elsewhere. A saline solution of crystalline epinephrine of animal origin, but containing no preservative or buffer produced, in previously inflamed sites, typical inflammatory reaction followed by necrosis. Passive transfer tests using the patient's serum, as in Case 1, were negative.

DISCUSSION

Lawson and Chambers[3] in 1931 reported the case of a white male asthmatic who, following subcutaneous injection of epinephrine hydrochloride 1-1000 solution, developed local lesions terminating in scarring and pitting. Duration of time between commencing epinephrine medication and occurrence of the phenomenon is not recorded. The lesions were found only at the sites of epinephrine injection, and the course of events beginning with a local wheal and ending in scarring took place in 10 to 14 days. Suppuration is not mentioned. These authors evidently believed the reaction was related to prolonged local vasoconstriction and tissue necrosis although they mention the possibility of local hypersensitivity or idiosyncrasy to the drug.

Cohen and Waterstone[2] report two cases of epinephrine sensitivity. In one, a Negro chronic asthmatic woman, after 6 years of self medication with epinephrine hypodermically, local reaction developed with aseptic inflammation, and healing with scarring and pitting followed at each site of injection. This was believed due to local tissue anaphylaxis (Arthus phenomenon). This patient also showed the Shwartzman phenomenon, in that, if a small amount of epinephrine was injected intravenously, activation of partially healed lesions took place. In the second case, also a Negro women, similar lesions were found. She was 39 years old at the time of reporting, and asthmatic from infancy, but the period at which these local inflammatory reactions began to occur is not mentioned.

Fig. 1.

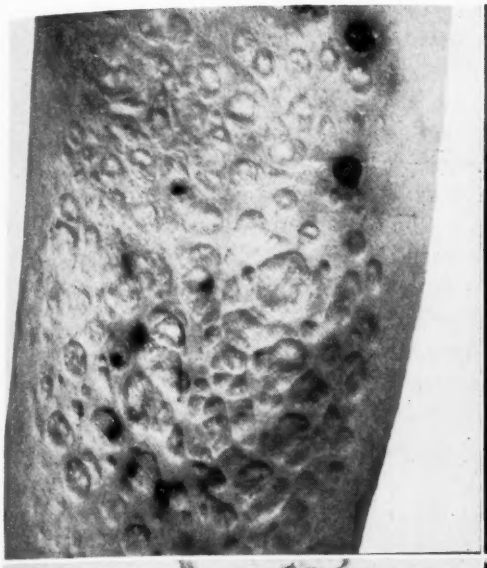

Fig. 2.

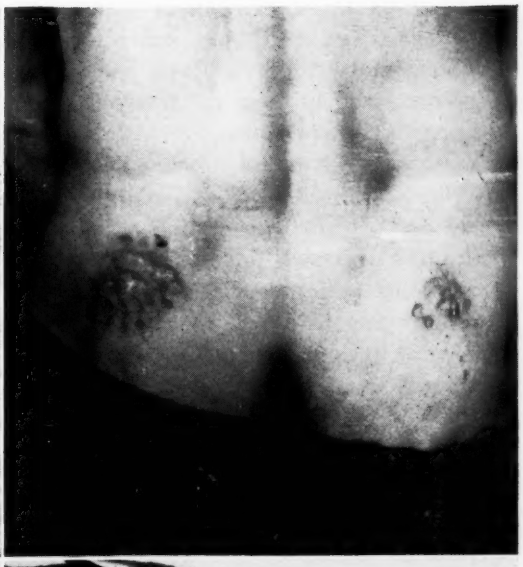

Fig. 3.

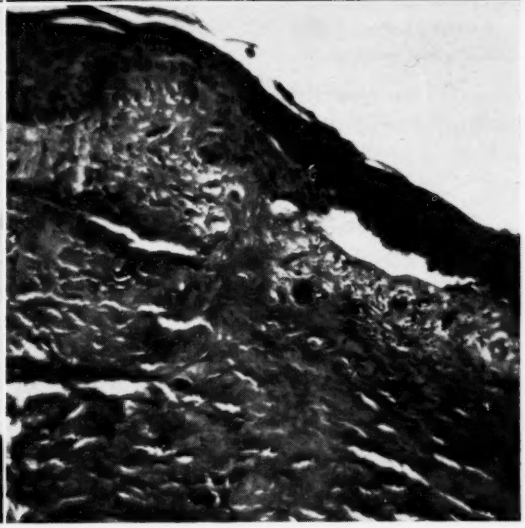

Fig. 4.

Fig. 1.—Case E. D. Photograph showing detail of site on upper arm where injections of epinephrine were given for several years. The black areas are healing inflammatory lesions following recent injections.

Fig. 2.—Case G. W. Photograph of gluteal regions, where injections of epinephrine have been given for several years, showing healed and healing lesions.

Fig. 3.—Case G. W.. Photomicrograph of skin, ×100, of 3-day-old lesions. Early intradermal epidermal necrosis with vesiculation; edema and degenerative swelling of collagen in subepidermal tissues. No eosinophils.

Fig. 4.—Case E. D. Photomicrograph of skin, ×100, of a 14-day-old lesion. Total necrosis of epidermis and corium with no appreciable inflammatory reaction.

Both these cases reacted similarly to a solution of Adrenalin 1-1000 (Parke, Davis & Co.) and a solution of epinephrine 1-1000 (Armour), and Adrenalin in oil. Neither was sensitive to synthetic epinephrine hydrochloride solution 1-1000 (Winthrop). It was shown that neither was sensitive to 0.5 per cent Chloretone or 0.1 per cent sodium bisulfate, the preservative and stabilizer, respectively, in these solutions. Both gave negative skin tests to beef and pork extracts. Passive transfer tests and interface precipitation tests with the sera of these patients did not show the presence of antibodies. The first patient developed very little relief from usual epinephrine solution; but synthetic preparations provided good relief of the asthma without local tissue necrosis. The authors believed that the local immune reaction (defensive mechanism) inactivated the epinephrine (antigen). Our cases obtained good subjective relief from epinephrine of animal origin. Cohen and Waterstone appear to be the first to have raised the question of the relationship to the Arthus phenomenon. Dumm[5] reported a case in which generalized urticaria, and asthma, followed hypodermic injection of epinephrine of animal origin. In this case synthetic epinephrine did not produce urticaria, or asthma. Herxheimer[6] reported urticaria following epinephrine injection.

Urbach[7] described a case with similar lesions. He attributed the reaction to a combination of intracutaneous epinephrine, and trauma at the site of injection. (His patient injected herself. She used a large needle and had a coarse tremor.)

Rowe reported four cases of cutaneous allergy due to extracted epinephrine and found that synthetic epinephrine could be used without reaction. In his cases self medication had been carried out for at least six years.

We believe our cases are the first in which attention is drawn to the fact that inflammation does not occur in areas where multiple injections have not been given over a period of time. Our failure to produce reactions in sites where epinephrine had not been previously given suggests that the reaction is a local fixed tissue one, in the skin. The phenomenon therefore is not exactly of the Arthus type, as Arthus produced his lesions in rabbits at any site, subcutaneously, following several weeks' preparation of the rabbit by subcutaneous or intraperitoneal injection of antigen (horse serum, milk).

It is important to note that in all the cases reported to date, a considerable period of use of epinephrine elapsed (1 to 6 years) before reactions occurred.

SUMMARY

Two cases, in addition to 8 previously reported, are described, in which local reaction to epinephrine of animal origin occurred. The use of the same site for inoculation over a period of time was found to be necessary for development of the phenomenon.

Absence of manifestations of sensitivity to artificial epinephrine and its derivatives was confirmed.

Absence of one cardinal feature of the Arthus reaction is emphasized.

It is suggested that the phenomenon is a type of local fixed tissue sensitivity.

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THE INHALATION TEST AS A DIAGNOSTIC PROCEDURE WITH SPECIAL EMPHASIS ON THE HOUSE DUST ALLERGEN

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INDUCED asthmatic attacks can be readily detected by the attending decrease in vital capacity and slowing in the expiratory rate and, in many subjects, these changes follow the inhalation of aerosolized allergenic extracts.[1, 2, 3] The method has been useful for the study of changes in the mechanics of respiration in bronchial asthma as well as for the study of drugs active in preventing or relieving symptoms.[4, 5, 6] The present report describes our experience with the inhalation method as a diagnostic procedure in a group of 75 asthmatic patients.

METHODS

The patients ranging in age from 6 to 62 years, with mild to severe asthma, were questioned carefully regarding the time of year in which symptoms occurred and the existence of precipitating factors. Skin tests were done by the intracutaneous method. All patients were exposed to aerosolized allergenic extracts in the manner described elsewhere,[2, 3] at a time when they were free, or almost free of asthma. The materials used included freshly prepared 5 per cent extracts of birch, oak, timothy, and ragweed pollens and the molds, alternaria, and hormodendrum. House dust extract,* prepared by the method of Boatner, Efron, and Dorfman,[7, 8] was used in a concentration of 1-400. Dosage was easily controlled by decreasing or increasing the number of inhalations. A satisfactory procedure was to give a single inhalation, followed in five minutes if no reaction occurred by three inhalations, and five minutes later by six inhalations, making a total of ten. Measurements of the vital capacity and expiratory rates were made at 1 or 1½ minute intervals during the test. A reduction in vital capacity of 10 per cent or more and/or a clearcut slowing in the rate of expiration accompanied or unaccompanied by symptoms and signs of asthma has been considered by us to be indicative of bronchial or pulmonary sensitivity to the substance inhaled. Care was taken to avoid nonspecific pulmonary reactions due to irritating extracts and a control consisting of the extracting solution was always included. If glycerinated extracts are used, it may be necessary, with certain patients, to dilute the extract and increase the number of inhalations. Induced pulmonary reactions may be readily relieved by the administration of a drug such as nebulized Isuprel. Very infrequently a pronounced induced pulmonary reaction, though promptly relieved, was followed later by

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asthma lasting for a few hours. Such an occurrence underscored the importance of the responsible allergen. Apprehensive patients may be upset by this, therefore they should be forewarned and should have suitable medication available.

RESULTS

The 75 patients were divided, as shown in Table I, into three groups: Group I including all those reacting to dust by inhalation, Group II including those reacting to other allergens but not dust, and Group III, those failing to react by inhalation to any of the allergens used. Group I was further divided into (A) those reacting to dust only and (B) those reacting to dust and one or more of the other allergens. Of the 75 patients, there were 57 who reacted to one or more allergens by inhalation. Dust caused reactions in 43 patients, ragweed in 22, birch in 5, and oak, timothy, alternaria, and hormodendrum in 3 each. The incidence of skin reactions was much greater than that of pulmonary reactions and the occurrence of a pulmonary reaction on exposure to an aerosolized allergen could not be satisfactorily predicted on the basis of skin tests. We were especially impressed, on the other hand, by our failure to produce pulmonary reactions with allergens which did not give skin reactions.

The time of year in which symptoms of asthma were aggravated as judged by the patient's statements and medical record is represented by the heavy bars in Figs. 1 to 4. As seen in Figs. 1 and 2, among the 43 patients reacting to dust by inhalation, in 25 asthma tended to be aggravated in the fall, especially during the month of October. On the other hand, patients failing to react to dust by inhalation but who reacted to other allergens (Fig. 3) showed a predominance of symptoms in September and earlier. Those who failed to react by inhalation to any of the 7 allergens used (Fig. 4) tended to have an aggravation of symptoms during the colder months.

As may be seen in Table II, there were no significant differences between the groups shown in Table I with regard to sex, age, and duration of asthma. However, patients in Group I and Group II had a high incidence of allergic manifestations other than asthma, as compared to Group III and this difference, statistically significant, is largely attributable to the high incidence of hay fever in the first two groups.*

DISCUSSION

The possibility that the observed pulmonary reactions are merely nonspecific and irritative in character must be considered. Nonspecific irritability of the lung, as measured by responsiveness to histamine or mecholyl, varies widely among asthmatic subjects and tends to be greatest among those having severe asthma.[9] However, the severity of asthma in our patients has not correlated well with the pulmonary responsiveness to inhaled aerosolized allergens, some of the patients with mild asthma having exhibited very marked pulmonary reactions. On the other hand, most of the patients falling in Group III, all of

*To test the data for statistical significance, we find Chi-square = 10.9 which, for 2 degrees of freedom, is significant at approximately the .005 level. Since better than 60 per cent of the total Chi-square was contributed by Group III, we conclude that this group shows a real difference in behavior from the other two.

TABLE I. CORRELATION OF SKIN AND INHALATION RESPONSES IN 75 ASTHMATIC SUBJECTS EXPOSED TO AEROSOLIZED ALLERGENIC EXTRACTS

ALLERGEN USED	PATIENTS REACTING TO DUST BY INHALATION												PATIENTS NOT REACTING TO DUST BY INHALATION							
	GROUP I												GROUP II				GROUP III			
	A PATIENTS REACTING TO DUST ONLY				B PATIENTS REACTING TO MISC. ALLERGENS AS WELL AS DUST				TOTAL PATIENTS A AND B				PATIENTS REACTING TO MISC. ALLERGENS				PATIENTS FAILING TO REACT TO ALLERGENS			
	SKIN		LUNG		SKIN		LUNG		SKIN		LUNG		SKIN		LUNG		SKIN		LUNG	
	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED	TESTED	RE-ACTED
Birch	20	4	9	0	10	6	8	3	30	10	17	3	11	5	8	2	12	1	7	0
Oak	21	3	9	0	11	6	7	3	32	9	16	3	11	3	7	0	12	1	7	0
Timothy	25	14	12	0	10	8	10	2	35	22	22	2	12	6	10	1	14	0	8	0
Alternaria	24	9	13	0	10	4	4	2	34	13	17	2	11	4	10	1	15	3	9	0
Hormodendrum	20	7	13	0	7	2	2	2	27	9	15	2	11	4	9	1	13	1	6	0
Ragweed	28	21	28	0	13	13	13	12	41	34	41	12	14	14	14	10	16	9	16	0
House Dust	30	30	30	30	13	13	13	13	43	43	43	43	14	10	14	0	16	12	18	0
No. of patients in each category	30				13				43				14				18			

GROUP I.(A)

DISTRIBUTION OF PATIENTS REACTING TO AEROSOLIZED DUST ONLY, INDICATING TIME OF YEAR WHEN ASTHMA IS AGGRAVATED

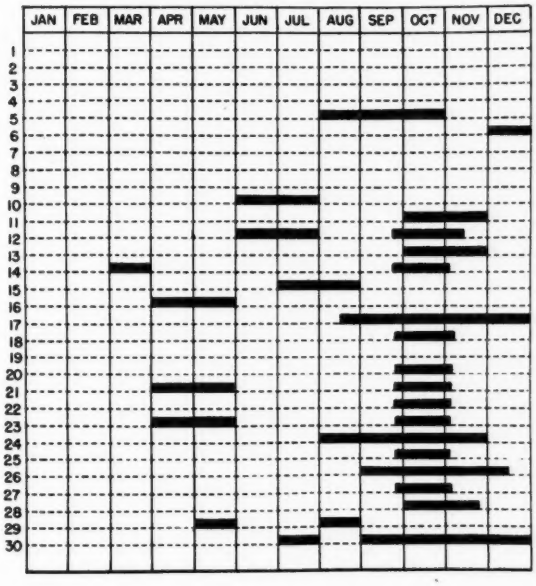

Fig. 1.

GROUP I. (B)

DISTRIBUTION OF PATIENTS REACTING TO MISCELLANEOUS ALLERGENS AS WELL AS DUST, INDICATING TIME OF YEAR WHEN ASTHMA IS AGGRAVATED

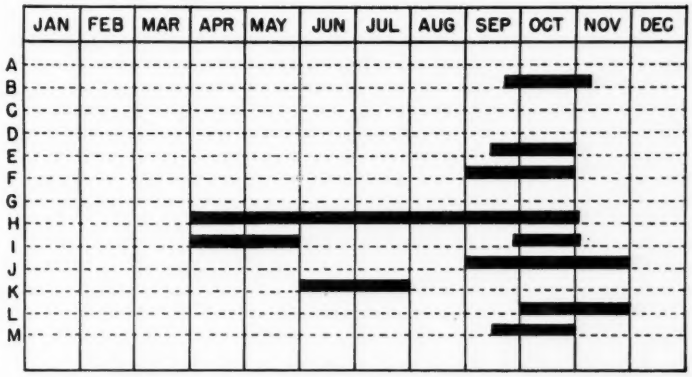

Fig. 2.

TABLE II. CLINICAL DATA ON 75 SUBJECTS WITH BRONCHIAL ASTHMA EXPOSED TO AEROSOLIZED ALLERGENIC EXTRACTS

	PATIENTS REACTING TO DUST BY INHALATION			PATIENTS NOT REACTING TO DUST BY INHALATION	
	GROUP I			GROUP II	GROUP IIII
	A PATIENTS REACTING TO DUST ONLY	B PATIENTS REACTING TO MISC. ALLERGENS AS WELL AS DUST	TOTAL PATIENTS REACTING TO DUST	PATIENTS REACTING TO MISC. ALLERGENS	PATIENTS FAILING TO REACT TO ALLERGENS
Numbers of cases	30	13	43	14	18
Males	17	4	21	7	8
Females	13	9	22	7	10
Age (Years)	6-58	14-49	6-58	8-62	6-62
Average Age (Years)	28	31	29	33	34
Duration (Years)	2-30	2-22	9 mos.-30	6 mos.-20	1 mo.-15
Average Duration (Years)	11	10	10	7	6
Pts. with Other Symptoms*	23	11	34	13	7
Hay Fever	18	9	27	11	4
Eczema	5	1	6	1	2
V.M.R.	2	4	6	3	2
Nasal Polypi	1	0	1	0	0
Urticaria	1	2	3	0	2
Family History Allergy	13	8	21	11	13

*Manifestations that may be of an allergic nature, past or present.

whom failed to exhibit pulmonary reactions to the inhaled allergens used by us, had severe asthma. These arguments also militate against the presence of histamine-like or acetyl-cholinelike substances in the extracts. Finally, pulmonary reactions to the inhaled allergens occurred only in those patients exhibiting skin sensitivity as well. We feel justified in concluding, therefore, that the occurrence of pulmonary reactions following the inhalation of aerosolized allergens cannot be ascribed to nonspecific reactions occurring in the lung.

In attempting to assess the value of the inhalation method as a means of diagnosis we are faced with the need for fixed points form which to take our bearings. We turn quite naturally to the two well-tried aids to diagnosis, the history and skin test. They are the best we have and, in a general way, these seem to be fairly trustworthy. In the individual case, however, we may be dependent on incomplete, and in some degree erroneous data buttressed by astute guessing, intuition, faith, and perhaps even bravado. Careful questioning revealed that our patients had symptoms intermittently throughout the year, that respiratory infections complicated the allergic picture in a disastrous manner, and that aggravation of asthma occasionally occurred in the absence of recognizable allergic or infectious causes. We quickly reached the conclusion that the methods of studying asthma and our understanding of the disease leave much to be desired. We are inclined to believe that we are not alone in this opinion.

We can not expect, therefore, to derive conclusive support for or evidence against the value of the inhalation method of diagnosis by consideration of the history and skin tests alone. We have derived some comfort, on the other hand,

GROUP II.

PATIENTS NOT REACTING TO DUST BY INHALATION BUT REACTING TO MISCELLANEOUS ALLERGENS, INDICATING TIME OF YEAR WHEN ASTHMA IS AGGRAVATED

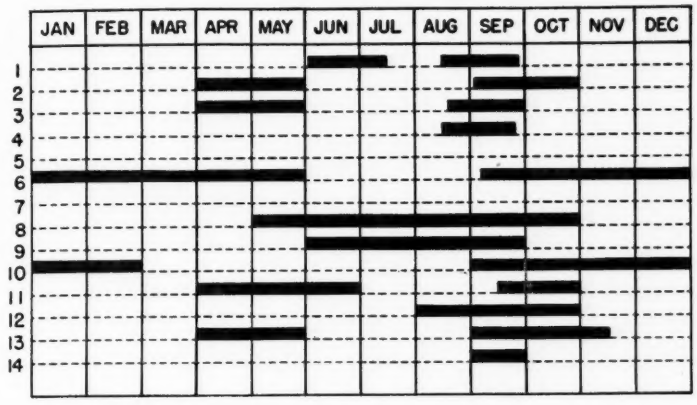

Fig. 3.

GROUP III.

PATIENTS FAILING TO REACT TO ALLERGENS BY INHALATION, INDICATING TIME OF YEAR WHEN ASTHMA IS AGGRAVATED

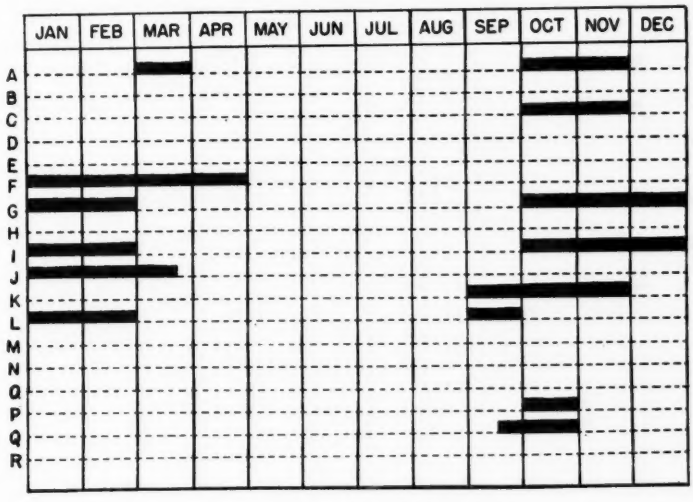

Fig. 4.

from the following considerations: first, that the procedure involves exposing a patient to a substance which might reasonably be expected to cause asthma in some subjects; second, that the reaction produced is indistinguishable from spontaneously occurring asthma except that it is usually much milder; and finally, that the reactions obtained, as mentioned above, cannot logically be ascribed to nonspecific irritation or due to the presence of histamine-like substances in the extracts.

Early in the course of this study our attention was centered on house dust because of the frequency of pulmonary reactions following exposure to this allergen in the laboratory among those who had increasing asthma in the latter part of September or in October, and the lack of such reactions when exposed to other allergens. Inspection of Figs. 1-4 clearly shows that, in patients who reacted to house dust by inhalation (Group I), house dust, among other possible excitants yet to be discovered, is a factor to be reckoned with in late September and October. The distribution of the patients in the other two groups was not unexpected. This "dust season," following so closely the period during which ragweed pollinates, at least in the New England area, has contributed to the confusion in the management of patients. This confines the dust season to a shorter period than that which has been considered to extend from late fall through the winter. Our findings have not only impressed us with the importance of dust as an allergen but have given us an understanding of those patients having exacerbations of asthma in the early fall.

SUMMARY AND CONCLUSIONS

1. Seventy-five asthmatic patients, studied from the point of view of history, skin reactions, and inhalation tests with pollen extracts of birch, oak, timothy, and ragweed, extracts of alternaria and hormodendrum and house dust extract, were divided into three groups: (a) patients in whom asthmatic attacks could be induced by inhalation of house dust extract; (b) patients in whom attacks could be induced with allergens other than house dust; (c) patients in whom attacks could not be induced by inhalation of the allergens.

2. The time of year when symptoms in each patient increased in severity was delineated month by month.

3. The clinical characteristics of the three groups are presented.

4. Support is given for the view that among the available methods for determining symptom-producing inhalants in bronchial asthma, the inhalation test is most valuable.

5. Sensitivity to house dust may be readily confused with ragweed pollen sensitivity. The results of this study indicate that, at least in the New England area, asthma occurring in the period between mid-August and mid-September is usually caused by ragweed pollen, whereas house dust is frequently the cause of symptoms from late September to the end of October. Asthma occurring from mid-August to the end of October probably arises from sensitivities to both ragweed pollen and house dust.

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THE EFFECT OF CORTISONE TREATMENT ON THE IN VITRO RELEASE OF HISTAMINE FROM SERUM AND BLOOD OF SENSITIZED RABBITS

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THERE have been many reports upon the usefulness of cortisone and ACTH in various allergic disorders. Bordley et al.,[1] Randolph and Rollins,[2] Rose,[3, 4] Samter,[5] Carryer,[6] and Carey[7] have demonstrated their effectiveness in asthma, hay fever, and urticaria. The mechanism whereby these hormones exert their influence is unknown. Since the allergic manifestation involves antigen-antibody reaction, many workers have attempted to study this response by observing the effect of cortisone and ACTH upon anaphylactic shock in the guinea pig. Leger, Leith, and Rose,[8] Friedlaender and Friedlaender,[9] Harris and Harris,[10] Malkiel,[11] and Landau,[12] all failed to observe from cortisone or ACTH any alleviating effect upon anaphylactic shock. Loveless[13] found no associated change in the concentration of sensitizing or of protecting antibodies after 14 days of ACTH therapy in one allergic individual.

The allergic reaction is now generally considered to be due to histamine or a histamine-like substance along with other metabolites. A study, therefore, has been attempted of the in vitro histamine release from (1) the blood of cortisone-treated sensitized rabbits exposed to the specific antigen and (2) from the blood of cortisone-treated normal rabbits exposed to a mixture of rabbit antiserum and specific antigen. Spain, Strauss, and Neumann[14] have previously shown that untreated allergic serum and antigen mixtures released histamine when added to normal rabbit blood whereas treated allergic serum and antigen mixtures did not release histamine. Carryer and Code[15] studied histamine release into rabbit plasma as a guage of antigen-antibody combination and detected no difference when cortisone was present. In their procedure they added cortisone only to the test tube mixture. In the following experiments cortisone was administered in large dosages to the rabbits before their blood was used.

PROCEDURE

Rabbits were sensitized with five intracutaneous injections of 10 ml. each of undiluted egg white every second day. One week after the last injection precipitins to egg white were observed by the micro-ring technique, usually with an antigen dilution of 1:20,000 or 1:50,000. Cortisone* was administered intramuscularly in total dosages ranging from 75 to 150 mg. over 2 to 4 day periods

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*A saline suspension of Cortone Acetate supplied by Merck & Co., Inc.

as shown in Tables I and II. Blood was withdrawn under nembutal anesthesia by cardiac puncture. Heparin, 0.09 mg. per ml. blood, was used as an anticoagulant. All glassware in which blood was placed was silicone coated.

Histamine was purified by the method of McIntire, Roth and Shaw[16] and determined by the method of McIntire, White, and Sproull[17] by reaction with 2,4-dinitrofluorobenzene. The only modification employed was that a Lumetron (Model 402E) Photoelectric Colorimeter with a mercury vapor lamp of high ultra violet transmission and a special auxiliary transformer was used with a M365 filter and 1 ml. micro cells. A Beckman spectrophotometer was not available. The adaption of the Lumetron proved completely satisfactory as gauged by recovery experiments of standard histamine added to normal blood.

In the first type of experiment, 5 ml. of antiegg white rabbit blood (pre- or postcortisone) were added to 2.3 ml. of egg white diluted 1:10 with saline and also to 2.3 ml. of saline (control). Control samples were run with each sample of blood analyzed since an appreciable amount of histamine, present normally in rabbit serum and increased under certain conditions, must be subtracted as a base from the amount found in mixtures of antiserum and antigen. Each of these mixtures was run in duplicate. After incubation at 37° C. for 30 minutes they were centrifuged. From the total supernatant of 4.8 ml., 2 ml. aliquots of each mixture were taken for the histamine determination.

In the second type of experiment, the serum employed was obtained from the sensitized rabbit not treated with cortisone. As the source of bound histamine, 5 ml. of normal rabbit blood or blood from an otherwise normal rabbit pretreated with cortisone was added to a previously incubated mixture of 0.4 ml. of antiegg serum and 0.4 ml. of egg white, 1:10. Saline was added to maintain the same volume as that in the first type of experiment and the rest of the procedure was as described above.

Seven rabbits were sensitized to egg white and their heparinized blood was used for study of in vitro histamine release after mixture with antigen. Both pre- and postcortisone blood samples were obtained in five rabbits. One rabbit died before treated and untreated blood samples could be taken so that two different sensitized animals were used in one pre- and postcortisone series. The sera of all these rabbits gave positive precipitin tests to egg white in a 1:20,000 dilution or more.

In an old egg white sensitized rabbit whose serum no longer contained precipitins to high dilutions of antigen there was no release of histamine.

RESULTS

From Table I it will be seen that an average of 1.8 gamma of histamine was released from mixtures of rabbit antiegg blood and egg white and an average of 1.4 gamma of histamine was released from mixtures similar except that the blood was taken after treatment of the animal with cortisone. Since there was no significant difference between these two sets of results under these experimental conditions, there was no evidence of inhibition of the histamine release as a result of cortisone therapy.

TABLE I. THE EFFECT OF TREATMENT WITH CORTISONE ON THE RELEASE OF HISTAMINE FROM MIXTURES OF SENSITIZED RABBIT BLOOD AND ANTIGEN

MIXTURES			GAMMA HISTAMINE		
				RELEASED BY ANTIGEN-ANTIBODY REACTION	
NO. ANTIEGG RABBIT BLOOD (5 ML.)	ML. EGG WHITE 1:10	ML. 0.85 PER CENT SALINE SOLUTION	IN TOTAL SUPER-NATANT	IN TOTAL SUPERNATANT	PER ML. BLOOD PLASMA
71	2.3	0.0	4.6	1.3	0.5
71	0.0	2.3	3.3		
71 PC-1	2.3	0.0	5.9	3.3	1.3 PC*
71 PC-1	0.0	2.3	2.6		
58	2.3	0.0	8.4	4.9	2.0
58	0.0	2.3	3.5		
58 PC-1	2.3	0.0	6.4	5.4	2.2 PC*
58 PC-1	0.0	2.3	1.0		
61	2.3	0.0	5.4	4.4	1.8
61	0.0	2.3	1.0		
61 PC-2	2.3	0.0	5.8	2.9	1.2 PC*
61 PC-2	0.0	2.3	2.9		
84	2.3	0.0	7.9	4.1	1.6
84	0.0	2.3	3.8		
53 PC-2	2.3	0.0	4.7	2.8	1.2 PC*
53 PC-2	0.0	2.3	1.9		
55	2.3	0.0	9.3	6.2	2.5
55	0.0	2.3	3.1		
55 PC-2	2.3	0.0	3.8	2.7	1.1 PC*
55 PC-2	0.0	2.3	1.1		
91	2.3	0.0	8.7	5.8	2.3
91	0.0	2.3	2.9		
91 PC-2	2.3	0.0	5.7	3.2	1.3 PC*
91 PC-2	0.0	2.3	2.4		

*PC—postcortisone
PC-1—total dosage of 75 mg. cortisone; 12.5 mg. every 8 hours for 2 days.
PC-2—total dosage of 150 mg. cortisone; 12.5 mg. per dosage for 4 days.

Table II shows the results obtained when normal heparinized rabbit blood or blood from an otherwise normal rabbit pretreated with cortisone was used as the source of bound histamine and only the serum from the sensitized animal and antigen were added to the blood. There was no inhibition of the histamine release by the use of blood from normal rabbits which were pretreated with cortisone.

DISCUSSION

There have been numerous reports on the efficacious results of cortisone therapy in hay fever, asthma, and other clinical allergic manifestations, with

TABLE II. THE EFFECT OF CORTISONE-TREATED NORMAL RABBIT BLOOD ON THE RELEASE OF HISTAMINE FROM ANTISERA AND ANTIGEN MIXTURES

MIXTURE				GAMMA HISTAMINE	
RABBIT ANTI-EGG SERUM 0.4 ML.	EGG WHITE 1:10 ML.	0.85 PER CENT SALINE SOL. ML.	RABBIT BLOOD 5 ML.	IN TOTAL SUPERNATANT	RELEASED IN TOTAL SUPERNATANT
#65	0.4	1.5	normal	4.1	1.2
#65	0.0	1.9	normal	2.9	
#65	0.4	1.5	No. 64 postcortisone	5.2	1.9
#65	0.0	1.9	No. 64 postcortisone	3.3	
#65	0.4	1.5	No. 59 postcortisone	5.1	2.0
#65	0.0	1.9	No. 59 postcortisone	3.1	

#64 and #59 rabbits received 100 mg. cortisone, 12.5 mg. every 6 hours for 2 days.

many attempts to explain it. In studying the influence of cortisone upon the antigen-antibody reaction, the majority of investigators have stated that cortisone has no apparent effect on anaphylactic shock or on the response of the sensitized smooth muscle to its antigen in in vitro preparations. Thus the evidence seems to indicate that there is no interference with the end result of the antigen-antibody reaction in the guinea pig. Since allergic and anaphylactic reactions seem to be produced by free histamine or histamine-like substances and other metabolites, the effect of cortisone upon histamine release in hypersensitive rabbits was studied. Some of us have previously shown that serum of a hay fever patient treated with ragweed injections when added to ragweed extract, did not release histamine under the same experimental conditions as the serum of an untreated hay fever patient and ragweed extract, which did release histamine from its bound form in normal rabbit blood. Our present results indicate that there is no demonstrable inhibition of the histamine release in mixtures of antiegg blood from rabbits treated with cortisone, and egg solution. Therefore, if there be an effect of cortisone on such hypersensitive conditions, it would seem to act beyond the stage at which histamine is released but before the onset of such pharmacological effects of histamine on the tissues as capillary dilatation, smooth muscle contraction or stimulation of the secretory glands. Therefore the relief from clinical allergic symptoms effected by cortisone in spite of no apparent inhibition of the antigen-antibody reaction nor inhbition of the histamine release, could conceivably be due to some type of alteration in the cement substance of the cell.

SUMMARY

1. When the blood of sensitized rabbits treated with large doses of cortisone was exposed to antigen, histamine was released in vitro in amounts comparable to that released under similar conditions from the blood of sensitized rabbits not treated with cortisone.

2. From the blood of rabbits, normal except for treatment with cortisone, histamine was released in the presence of rabbit antiserum and antigen to the same degree as from the blood of normal rabbits not treated with cortisone.

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TIME OF DAY OF POLLEN SHEDDING OF SOME HAY FEVER PLANTS

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POLLEN shedding and dispersal is of particular scientific interest to the botanist and the plant breeder in their consideration of the phenomena of pollination, fertilization, and seed setting. But this subject is also of interest to the medical profession in the treatment of asthma and pollinosis.

The present study grew out of a plant breeding investigation aimed at determining the time of day when grasses shed pollen. This information is needed by plant breeders as a basis for collecting large quantities of viable pollen and for making hybridizations in the field at the time when there is the least danger of contamination by foreign pollen in the air.

The same information might be useful to the medical profession in the collection of large quantities of pollen for use in clinical medicine.

Surface reactions caused by pollen, such as hay fever, asthma, and dermatitis of the exposed parts, vary in intensity at different seasons, during different weeks of the same season, and at different times during a given day.[2] Numerous kinds of pollen may be present in the air at once, but usually only a few of them will be of any significance as hay fever agents.[11]

Numerous reports are available in the literature relative to the time of day certain species shed pollen. However, most of these reports are based on observation rather than experimental measurement of the amount of pollen liberated hourly from plants during the day.

Knuth[10] summarizes the observations of numerous workers in his monograph "Handbook of Flower Pollination." In general the reports of time of day of pollination are in fair agreement, but numerous exceptions can be found where investigators report entirely different times of the day for pollen shedding for a species in the same region.

Jensen and Bøgh[7] made counts of the number of pollen grains caught on petroleum jelly-coated microscope slides which were exposed at various intervals during the day. They found this scheme of determining time of day of pollen shedding to be very acurate.

In a study of 29 grasses at Lincoln, Neb., in 1944 and 1945, Jones and Newell[8] used a similar technique and found that most of the grasses required 2 to 6 hours in each of several successive days for the completion of pollen shedding. When meteorologic conditions were optimum for blooming, these daily pollination periods occurred rather regularly at the same time of day for any specific grass. Before or after this short period of active shedding, little pollen was present in the air, even in the center of the grass field. Daily pollen shedding occurred partially or entirely during periods of darkness for thirteen of the grasses studied. Others normally shed pollen in daylight.

The assumption that the presence of excitants is a common characteristic of all grass pollen seems warranted from numerous tests.[1] In general, the

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self-fertilized grasses, such as wheat, barely, and oats, and the grasses (including corn) which produce the larger and less buoyant pollen, are not considered of great importance as excitants. The relatively small, buoyant pollen grains of widely distributed grasses, such as Kentucky bluegrass, Timothy, and Bermuda grass, have been listed as the most important in contributing to the hay fever malady.

Geisler,[6] described the general characteristics of grass pollen and presented drawings of pollen from 32 different grasses obtained from mounted herbarium specimens. She studied grasses from four habitats, viz., aquatic, wet lowland, mesophytic, and prairie. She reports that the pollen of prairie grasses is markedly larger than that of more moist habitats with the exception of the pollen of *Zizania aquatica,* which is similar in size to the pollen of andropogon and Sorghastrum. This fact made it impossible to separate prairie from aquatic grasses on the basis of pollen size differences.

Results of studying pollen from the same grass stand in two different years indicate that pollen size may vary as a result of environmental conditions.[9] Seventeen of 31 grasses produced pollen with no significant size variation between the two years, 5 showed significant differences at the 5 per cent level and 8 showed significant differences at the 1 per cent level. Thus seasonal environment has a pronounced effect on the pollen size of some grasses.

In a recent series of articles, Durham[3-5] reported the specific gravity, rate of fall, and size of pollen of numerous species of plants causing hay fever.

METHODS

Forty-five species of plants were studied at Lincoln, Neb., in 1945 and at Stillwater, Okla., in 1946 and 1947, to determine pollen size and the time of day and time of year that pollen shedding occurred. The species studied are given in Table I.

Pure samples of pollen were collected from each plant and stored in glycerine-alcohol solution. Measurements of pollen diameters were made from permanently mounted slides according to the method described by Jones and Newell.[9]

To determine the time of day a species sheds its pollen, four microscope slides which had an area of one square inch coated with a thin film of petroleum jelly were exposed at elevations near the height of the plant in the center of the selected area. The slides were placed in holders that were attached to weather vanes at an angle of 45° (Fig. 1). This method of exposure kept the petroleum jelly-coated side of the slide exposed against the prevailing wind and facilitated catching the pollen that was impinged against the slide, whether it was blown through the air or fell as a result of gravity. The total number of pollen grains on 10 random low-power microscope fields (16 sq. mm. area) per slide was used as a measure of the amount of pollen shed.

Close observation of the anthers previous to blooming made it possible to predict when pollen shedding might be initiated by a given species. For these

studies, preliminary exposures were made every five to six hours during the first days when the investigation of a species was begun. After the general time of day when pollen was being shed from the anthers was determined, intensive studies were continued for two to six days. Exposures were made at 30 minute intervals during the period of active pollen shedding. When microscope examination revealed no pollen was being caught on the slides, the 30 minute time exposures were discontinued. Slides were left exposed until the following day, so that counts of pollen could be made for each 24 hour period, as well as for periods of several days. The counts made at 30 minute intervals were recorded on the basis of central standard time.

Aids used in identifying pollen included size and shape measurements, knowledge of which kinds of plants were shedding pollen at the same time of year, the time of day that each plant sheds its pollen, and the mass effect of the pollen under study. Permanent mounts of different pollens were also used for comparison.

Fig. 1.—A weather vane with microscope slide holder attached, as used in this study. Grass plants in background.

EXPERIMENTAL RESULTS

Shape, Color, and Size of Pollen.—The pollen of grasses is characterized by a somewhat spherical shape and yellowish color. Its form varies from the ellipsoidal shape of rye pollen to the almost spherical shape representative of

TABLE I. CLASSIFICATION OF 45 SPECIES ACCORDING TO DIAMETERS OF POLLEN GRAINS AND TIME OF DAY AND SEASON OF POLLEN SHEDDING FROM MEASUREMENTS AND OBSERVATIONS MADE IN THE SEASONS OF 1945 AT LINCOLN, NEBRASKA, AND 1946 AND 1947 AT STILLWATER, OKLAHOMA.

BOTANICAL NAME	COMMON NAME	MEAN DIAMETERS AND STANDARD ERRORS IN μ*	TIME OF DAY OF POLLEN SHEDDING	GENERAL SEASON OF POLLEN SHEDDING
		I. Diameters of 20 to 30 μ		
Alopecurus carolinianus	Swamp foxtail	28.4 ± 0.1	5-8 P.M.	May, June
Ambrosia trifida†	Giant ragweed	20.1 ± 0.2	7 A.M.-1 P.M.	Aug., Sept., Oct.
Ambrosia psilostachya‡	Western ragweed	25.0 ± 0.4	7 A.M.-1 P.M.	Aug., Sept., Oct.
Calamagrostis epigeios		27.3 ± 0.6		June, July
Eragrostis trichodes	Sand lovegrass	26.3 ± 0.4	7-11 A.M.	Aug., Sept.
Phragmites communis	Common reed	26.4 ± 0.4	6-10 A.M.	Aug., Sept.
Poa pratensis	Kentucky bluegrass	28.4 ± 0.9	3-8 A.M.	May, June
		II. Diameters of 30 to 40 μ		
Andropogon ischaemum	Yellow bluestem	33.6 ± 0.8		Aug., Sept.
Andropogon saccharoides	Silver beardgrass	34.2 ± 0.7		Aug, Sept.
Arrhenatherum elatius	Tall oatgrass	37.6 ± 0.4	3-7 P.M.	May, June
Bouteloua curtipendula†	Side-oats grama	35.7 ± 0.5	4-9 A.M.	July, Aug., Sept.
Bouteloua gracilis	Blue grama	30.8 ± 0.6	3-9 A.M.	July, Aug., Sept.
Buchloe dactyloides	Buffalograss	37.4 ± 0.7	6-11 A.M.	May, June
Dactylis glomerata	Orchardgrass	36.2 ± 0.3	4-10 A.M.	June, July
Festuca elatior†	Meadow fescue	37.4 ± 0.7	3-8 P.M.	June, July
Festuca ovina	Sheep fescue	35 4 ± 0.7	4-8 P.M.	May, June
Kochia scoparia	Mexican firebush	33.1 ± 0.5	7 A.M.-4 P.M.	July, Aug., Sept.
Koeleria cristata	June grass		3-7 P.M.	May, June
Phalaris arundinacea	Reed canarygrass	37.5 ± 1.2		June, July
Phleum pratense	Timothy	36.6 ± 0.9	4-9 A.M.	June, July
Stipa viridula	Green needlegrass	35.0 ± 0.6		May, June

		III. Diameters of 35 to 50 μ		
Andropogon furcatus	Big bluestem	40.2 ± 0.6	4-7 A.M.	Aug , Sept.
Andropogon hallii	Sandhill bluestem	40.2 ± 0.9	4-9 A.M.	Aug , Sept.
Agropyron cristatum	Crested wheatgrass	43.0 ± 0.6	2-6 P.M.	May, June
Agropyron elongatum	Long-spiked wheatgrass	45.5 ± 0.7	2-6 P.M.	June, July
Agropyron intermedium	Intermediate wheatgrass	49.1 ± 1.3	2-6 P.M.	June, July
Agropyron repens	Quackgrass	45.1 ± 0.6	2-6 P.M.	June, July
Agropyron smithii	Western wheatgrass	47 5 ± 0.6	2-6 P.M.	June, July
Bromus inermis	Bromegrass	42.1 ± 0.7	2-7 P.M.	May, June
Elymus junceus	Russian wildrye	43.7 ± 0.9	3-7 P.M.	May, June
Elymus virginicus	Virginia wildrye	43.6 ± 0.6		June, July
Hordeum jubatum	Squirreltail	43.9 ± 0.1		May, June
Hordeum pusillum	Little barley	38.7 ± 0.8		May, June
Panicum virgatum	Switchgrass	39.2 ± 0.8	10 A.M.-2 P.M.	July, Aug., Sept.
Sorghastrum nutans	Indiangrass	44.5 ± 0.6	6-10 A.M.	Aug., Sept.
Sorghum vulgare	Sorghum	45.4 ± 0.8	4-10 A.M.	Aug., Sept.
Sorghum vulgare sudanense	Sudan	48.1 ± 0.7	6-12 A.M.	Aug., Sept.
Spartina pectinata	Sloughgrass	37.3 ± 0.7	4-10 A.M.	Aug., Sept.
Tripsacum dactyloides	Gamagrass	43.7 ± 0.5		July, Aug.
		IV. Diameters of 45 to 65 μ		
Avena sativa	White oat	50.6 ± 0.9		May, June
Secale cereale	Balbo rye	54.4 ± 1.4	3-11 A.M.	May, June
Triticum vulgare	Pawnee hard wheat	56.7 ± 0.8	4-10 A.M.	May, June
		V. Diameters of 80 to 100 μ		
Zea mays†	Yellow dent corn	93.0 ± 1.1	7 A.M.-2 P.M.	July, Aug.
Zea mays	Popcorn	99.5 ± 0.8	7 A.M.-2 P.M.	July, Aug.
Zea mays†	Sweet corn	94.2 ± 0.5	7 A.M.-2 P.M.	July, Aug.

*All measurements made on grains expanded in glycerine-alcohol solutions according to method described in Reference 2.
†Studied at both Lincoln, Neb., and Stillwater, Okla.
‡Studied only at Stillwater, Okla.

most of the grasses studied. The color of the pollen varies from a deep yellow in some varieties of corn to an almost colorless condition in swamp foxtail, with the pollen of most grasses having a creamy to yellowish color. Because of the similarity of the various kinds of grass pollen, neither shape nor natural color appear to be of value in identifying pollen of the different grass species causing hay fever.

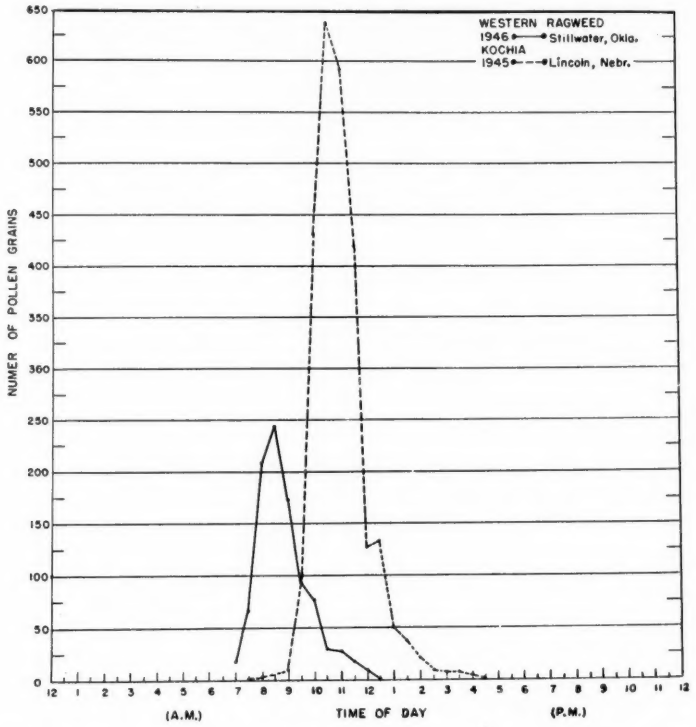

Fig. 2.—Time of day of pollen shedding of Kochia at Lincoln, Nebraska during 1945, and of western ragweed at Stillwater, Oklahoma, 1946.

Diameter measurements of pollen were made in an effort to identify and to determine buoyancy of pollen of different species. The mean diameters of pollen varied from 20.1 ± 0.2 μ for giant ragweed to 99.5 ± 0.8 μ for popcorn with 32 of the 45 species having pollen grains between 30 and 50 μ (Table I). Diameter of pollen is related to size and rate of fall.[5] Durham[3, 4] gives the specific gravity and experimental rate of fall when compared to short ragweed of eight species which were studied in the present investigation. According to his results and the size measurements made in this study, the small pollen grains of low specific gravity, such as giant ragweed and western ragweed fall more slowly than the large heavy pollen of rye and corn. Mexican firebush, Kentucky bluegrass, Orchard grass, and Timothy were intermediate in rate of fall.[4]

Time of Day of Pollen Shedding.—It should be emphasized that observation alone is not always completely reliable to determine the time of day and

the number of days that species shed pollen. With some plants which are not prolific pollen producers, the exposure of slides has proved the inadequacy of casual observation.

Thirty-five species were studied to determine the time of day they shed pollen. The data are summarized in Table I; however, six species, which were considered representative of the entire group, are discussed in detail. These species include Mexican firebush, smooth bromegrass, giant ragweed, western ragweed, sweet corn, and rye.

Mexican firebush: Kochia or firebush is an escaped ornamental that is becoming a serious hay fever and weed pest in the north central United States. It produces large quantities of pollen from July 10 to September 10 at Lincoln, Nebraska, and is prevalent in nearly all fields and waste places.

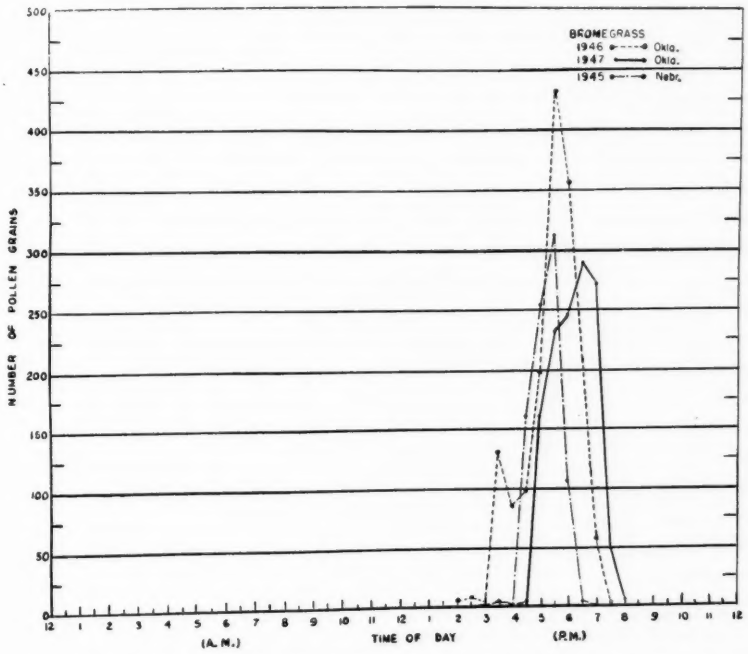

Fig. 3.—Time of day of pollen shedding of bromegrass at Lincoln, Nebraska in 1945 and at Stillwater, Oklahoma in 1946 and 1947.

The seriousness of Kochia as a hay fever plant was brought to the attention of the author by a colleague. He made trips daily at about 10:00 A.M. to experimental plots in the field. Each day during pollen season he would develop severe symptoms of hay fever following his field visits. A study made in 1945 at Lincoln, Nebraska, showed that Kochia shed 94 per cent of its average daily total pollen between 9:00 A.M. and 12:30 P.M., with the peak of shedding occurring at 10:30 A.M. (Fig. 2). Very little pollen was caught on exposed slides after 2:00 P.M. On the basis of these data, my colleague was advised to visit the experimental plots after 2:00 P.M. each day. This change in his schedule resulted in his having very light symptoms of hay fever.

Smooth bromegrass: The dispersal of smooth bromegrass pollen was studied for six days at Lincoln in 1945. On the average, it required only 15 minutes after blooming until the anthers started dehiscing and shedding pollen. Pollen grains of bromegrass are only 42.1 ± 0.7 μ in diameter and are very buoyant. In a few minutes after maximum blooming, "clouds" of yellow pollen were observed as breezes swept across the field. These observations were substantiated by data obtained from slides exposed for 30 minute periods. Pollen was caught on the slides from 2:30 to 7:00 P.M., but 99.5 per cent of the average daily total was shed between 4:00 and 6:30 P.M. (Fig. 3).

Temperatures of 80° to 85° F. were found to be optimum for the blooming of this grass; however, active blooming has been observed at temperatures between 74° and 90° F. Temperatures lower than 70° F. inhibited blooming on June 14 and 15, 1945.

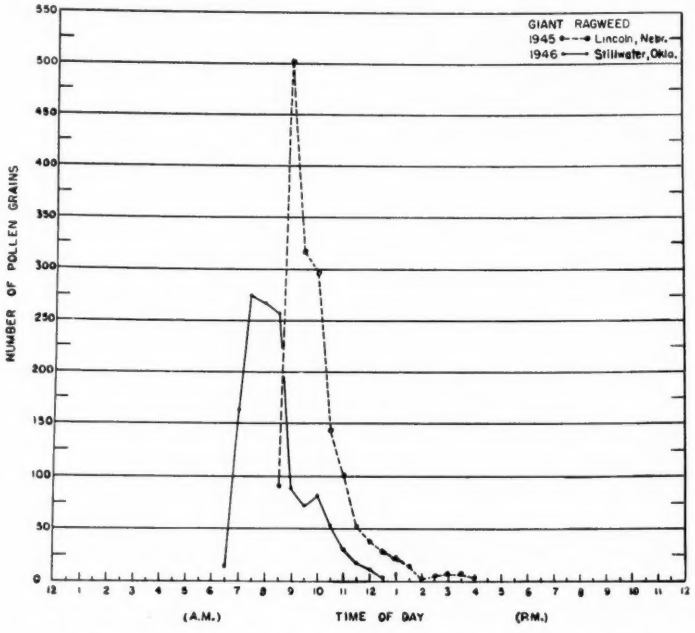

Fig. 4.—Time of day of pollen shedding of giant ragweed at Lincoln, Nebraska, in 1945 and at Stillwater, Oklahoma in 1946.

Records of bromegrass pollination at Lincoln for the period 1936 through 1945 show the seasonal pollen shedding occurring in late May or early June. The pollen season lasted only for 11 days in 1944 and for 14 days in 1945. Bromegrass produces a tremendous amount of pollen and is grown on a large acreage, and therefore, is a hay fever problem for a short period each season. However, since its daily pollen shedding period is confined to a short period in late afternoon, it is possible to avoid exposure to the air-borne pollen.

Slide exposures were made on four days in the second and third weeks of May in 1946, and during early June in 1947, for the investigation of daily pollen shedding of bromegrass at Stillwater, Oklahoma. The majority of pollen in both years was caught during the late afternoon and early evening (Fig. 3).

The days on which studies were made in 1947 were warmer than those in 1946. Clear skies, low relative humidity, and strong winds were common. The temperatures between noon and 4:00 P.M. increased each successive day from June 4 to June 9, inclusive. Likewise, the time of maximum daily pollen shedding each successive day was consistently later by approximately 30 minutes. Apparently the delay in maximum shedding on successive days was due to rather complete blooming and shedding each day; thus, a little more time was required for growth and maturation of the anthers for the next day's pollen supply. Even though optimum temperatures for blooming and shedding of approximately 86° F. prevailed near noon each day, no shedding occurred at that time. Apparently the duration of light and heat had not been sufficient by then to mature the anthers. The time of day of pollen shedding was found to be a little later at Stillwater, in 1946 and 1947 than at Lincoln in 1945.

Giant ragweed: Giant ragweed is one of the heaviest producers of pollen of any species known to cause hay fever. It is fortunate that this species is restricted to certain soil sites and thus is not widespread in most regions. Pollen shedding was studied on Aug. 24 and 25, 1945 at Lincoln. Eighty-eight per cent of the average daily total was shed between 8:00 and 11:00 A.M. (Fig. 4).

Studies were conducted at Stillwater on Sept. 5, 6, 9, and 11, 1946. Pollen shedding was initiated earlier in the day than at Lincoln. About 95 per cent of the average daily total of pollen was shed between 7:00 and 10:30 A.M.

The pollen season at Lincoln in 1945 extended from August 4 to September 30, with the peak occurring between August 24 and September 3. At Stillwater in 1946, the pollen season lasted from August 1 to October 10, with the peak between September 14 and 24. The principal effect of latitude appeared to be on dates rather than on length or severity of the pollen season.

Rainfall on the morning of September 10 delayed pollen shedding for approximately two hours. Apparently the amount of pollen shed on September 10 was only slightly less than normal.

Western ragweed: Western ragweed is a perennial of widespread distribution in the Corn Belt and Great Plains. It normally produces a large daily quantity of pollen from July 1 to September 15, with the peak of production occurring about August 15 to 30 at Stillwater.

As an average for three days in September 1946, pollen shedding extended from 6:30 A.M. to 12:30 P.M., with the period of maximum shedding at 8:30 A.M. Approximately 90 per cent of the average daily pollen supply was shed between 7:00 and 10:00 A.M. (Fig. 2).

Rain delayed pollen shedding for two hours on September 10. After the relative humidity returned to normal, tremendous quantities of pollen were shed about 10:30 A.M.

Sweet corn: The first few pollen grains were caught between 6:30 and 7:00 A.M. on slides exposed in the center of a field of sweet corn for four days in late June and early July in 1946. The rate of pollen shedding increased rapidly until the maximum was reached between 7:30 and 8:00 A.M. (Fig. 5).

Slide studies were made on June 23, 24, and 25 in 1947. Meteorological conditions and the daily pollination cycles were very similar on each of these days. Heavy shedding extended from 8:00 to 11:00 A.M., with the peak of pollen shedding occurring between 8:30 and 9:00 A.M.

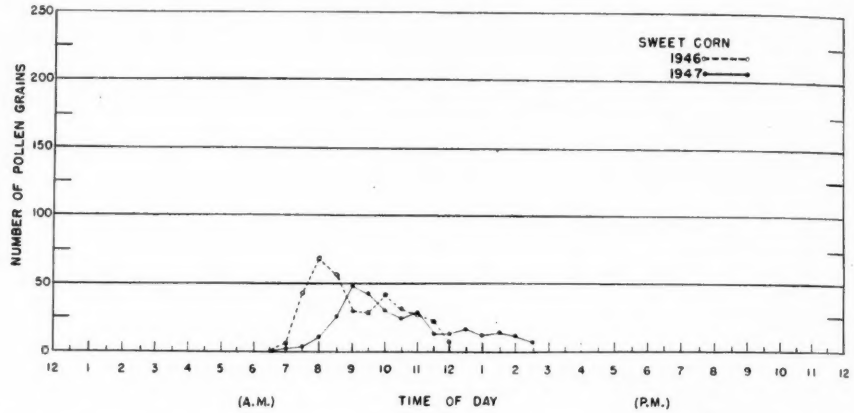

Fig. 5.—Time of day of pollen shedding of sweet corn at Stillwater, Oklahoma in 1946 and 1947.

The maximum rate of pollen shedding occurred an hour earlier in 1946 than in 1947, apparently because of lower relative humidities and higher temperatures in the early morning on the days of study in 1946.

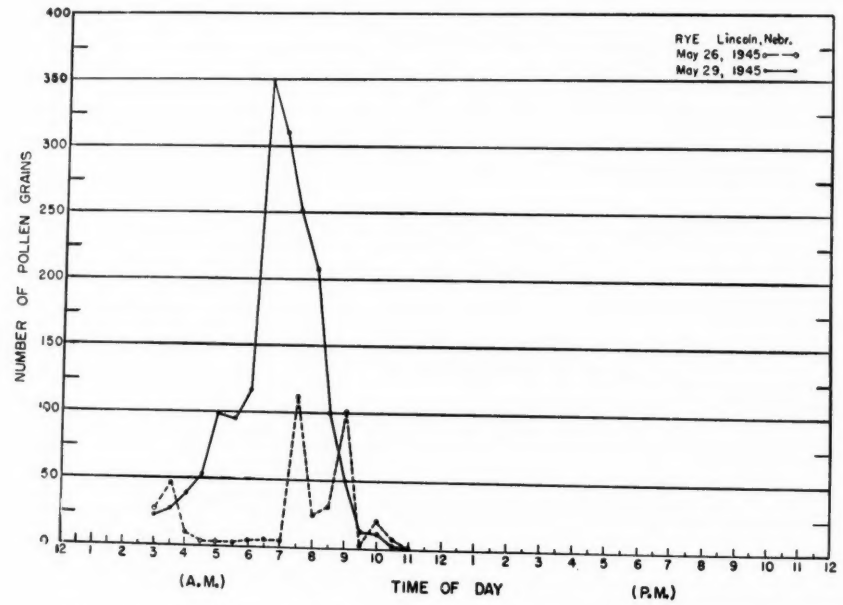

Fig. 6.—Time of day of pollen shedding of rye at Lincoln, Nebraska in 1945.

Sweet corn pollen was found to be 94.2 ± 0.5 μ in diameter in 1947 and appeared to be the least buoyant of any grass pollen. Even though sweet corn

and field corn are planted on large acreages, the number of plants per acre is small and they have not proved to be serious hay fever pests. The daily pollen production was shed in a short period (Fig. 5).

Rye: The effect of wind on the dispersion of rye pollen was studied on May 26 and 29, 1945. It was necessary to begin exposures of slides before dawn to determine the extent of pollen shedding. Slides were placed on the ground so that the number of pollen grains which fell could be compared with the number caught on slides exposed at the height of the plants.

During 30 minute periods on May 26 when light breezes swept across the field a large number of pollen grains were caught on the aerial slides. Only a small number was caught during periods of calm. Considerable variation is shown in the number of pollen grains caught during different 30 minute intervals of this relatively calm day (Fig. 6). Almost four times as many pollen grains were caught on the ground exposures as on the aerial exposures.

A wind velocity of 7 m.p.h. on May 29 resulted in the pollen being dispersed immediately upon dehiscence of the anthers. The data indicate an increase in the amount of pollen shed each 30 minute period until the peak of production was reached at 6:30 A.M. A rapid decrease in amount occurred until shedding ceased around 11:00 A.M. (Fig. 6). Considerably less pollen was deposited on the slides exposed on the ground on May 29 than on May 26. Thus more pollen is dispersed into the air on windy days, which probably is the reason hay fever susceptibles often are more uncomfortable on such days.

Other species: Related species within a genus were characterized by similar pollen shedding habits (Table I). Blooming and pollen shedding occurred at approximately the same time of the day for five species of wheatgrasses, as well as for the closely related Russian wild rye. Species within the genera, Ambrosia, Andropogon, Bouteloua, Festuca, and Sorghum also tended to shed pollen at similar times of the day and year.

DISCUSSION

The major factors contributing to a plant's importance as a hay fever pest are length of season of bloom, abundance of pollen, intensity of pollen production and buoyance of the pollen. The small pollen grains of Mexican firebush, smooth bromegrass, giant ragweed, and western ragweed, all heavy pollen producers, are very buoyant and easily dispersed by wind. The pollen of rye is considerably larger and less buoyant. Corn and sweet corn have the largest and least buoyant pollen of any grass.

A determination of the time of day of pollen shedding for the different hay fever species in a given region would aid materially in associating a patient's hay fever symptoms with certain species. Also, a measure of the amounts of pollen produced in different geographic regions by a species or by different species should throw light on the subject of why some treatments fail in one region and not in another.

SUMMARY AND CONCLUSIONS

1. Investigations were conducted to determine size of pollen and the time of day and time of year of pollen shedding of 45 species of plants when grown at Lincoln, Neb., in 1945 and Stillwater, Okla., in 1946 and 1947.

2. Mean diameters of pollen grains are reported as an aid in determining pollen size and buoyancy.

3. A determination of the time during each day when a species sheds pollen will facilitate the collection of large quantities of pollen for use in clinical medicine.

4. Petroleum jelly-coated microscope slides were so exposed as to intercept air-borne pollen. The number of pollen grains caught during 30 minute intervals per 16 sq. mm. area was used as a measure of the amount of pollen shed. This means of pollen collection gives a reliable estimate of the relative amounts of pollen produced and dispersed by species at various intervals during the day.

5. Between 90 and 99 per cent of the pollen shed was liberated by most species within a short period of three to four hours each day. The time of day of shedding varied widely for the different species and appeared to be controlled by factors inherent in each species.

6. The effects of environmental factors on pollen shedding were considered. Temperatures of less than 60° F. inhibited shedding in some species. Wind movement was important in speeding up anthesis, dehiscence, and disperal. High relative humidity delayed pollen shedding, but did not inhibit it.

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QUANTITATIVE STUDIES OF AIR-BORNE FUNGI OF HAVANA IN EACH OF THE TWENTY-FOUR HOURS OF THE DAY

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SERIAL hourly fungus studies have for their object, the analysis of the fungus content of the air of a locality during each of the twenty-four hours of the day. These studies cannot be made daily over a great length of time, if the Petri dish method is employed, on account of the excessive and tedious labor involved in the manipulation of hundreds of plates, but can be repeated once a week or in determined months of the year in order to obtain an exact idea of the behaviour of fungi under determined meteorologic influences such as wind, rain, humidity, the degree of cloud coverage, and variations between day and night hours, etc.

In 1939, we published[1] an investigative article showing the hourly variations which the fungus content of the atmospheric air underwent with relation to meteorologic changes, and their influence in certain instances of asthma and rhinitis.

This work was carried out by exposing to the air, for a quarter of an hour, Petri dishes with appropriate culture media.

The plates were exposed every hour, day and night, arranging them so that the prevailing winds blew freely over them. The numbers of colonies per dish were then plotted in curves (Fig. 1) with comparisons, taking into consideration temperatures, barometric pressures, relative humidity, wind velocity and direction, and cloud coverage.

The strict correspondence between the colony curve and wind velocity is obvious, the colony curve descending with diminution of wind velocity and ascending when wind velocity was at its height.

If we fix our attention on the curve of the number of colonies, we see that the colonies on the plates increase during daylight hours, and diminishes during nocturnal hours. In considering this point, it brought us to the conclusion that the actual quantity of fungi in the air is greater during the day than during the night. After further voluminous air studies we have reached totally reversed conclusions when we employed methods of studying the fungi of the air which eliminate the factor of wind velocity. The cause of the initial error lay in the fact that the Petri dishes were exposed to the air attempting always to face them to the prevailing wind. In this manner the number of fungus spores was influenced by the amount of air which flowed directly over the dishes, the greater the volume of air, the larger the number of colonies deposited.

*Translated by I. S. Kahn, M.D.

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This brought us to the conclusion that quantitative studies of fungi based on the open exposure of dishes to circulating air alone, will determine a quantity of fungus spores, depending on the velocity of the wind. But this is incorrect when it is desired to appraise the number of fungi in a given volume of air.

It is common to notice that asthmatics sensitive to fungi commence to notice symptoms of discomfort as evening comes on, at night, or around dawn. In day hours their annoyance is less. It is recognized that individuals allergic to fungi become worse when they inhale the dust from pillows and mattresses infected with causative fungi or when compelled to sleep in damp quarters with walls infected with such organisms. How then could we explain the symptom increase as evening comes on precisely when our initial studies indicated a diminution of the fungus content of the air?

At first we might consider that this nocturnal symptom increase coincident with the lowered fungus count could be due to a variation of the allergic reactivity or some other physiologic factor, a possible, but unconvincing hypothesis. From this discrepancy came the idea of working with stationary air and eliminating the factor of wind velocity.

Feinberg and Steinberg[2] had studied (1939) the pollen content of the air, by experimenting with a determined volume of air using a sack (or box) with a volumetric capacity of a tenth of a cubic yard, whose bottom was completely covered with microscopic slides covered with petroleum jelly. This was carried to the open air, opened and kept opened for 2 or 3 minutes to permit free air interchange, and then closed, sealed and kept all night in a quiet spot in order that all the pollen contained in that volume of air should be deposited on the slides.

The total number of pollen grains on all the slides was counted giving the pollen content of 0.1 cubic yard of air; by multiplying this by ten was obtained the number of pollen granules per cubic yard.

In applying this method to the study of mold spores, we designed a four sided wooden box or cabinet with an inside length of 60 centimeters and width and depth of 15 centimeters. This apparatus had 2 doors (Fig. 2) opening the whole length of the sides, to permit the free entry of air into the apparatus. The doors closed with automatic latches and all the joints between the boards forming the sides, and even the doors themselves were hermetically sealed to prevent air currents from disturbing the findings.

Before use, the internal surfaces of the apparatus must be cleaned with a pledget of cotton moistened with a solution of 1:1000 Merthiolate. The box is then carried to the open air, the two doors are opened wide and it is left in this manner for 2 or 3 minutes. One door is then closed and through the other is placed, deep in the apparatus, an open Petri dish with an appropriate culture medium. The second door is then closed. Meanwhile the lid of the Petri dish is kept face down on top of the apparatus.

All this manipulation must be done rapidly, but care taken not to close the doors with a violent slam which would introduce air currents in the wooden box. When an hour has passed, one door is opened, and the cover of the Petri

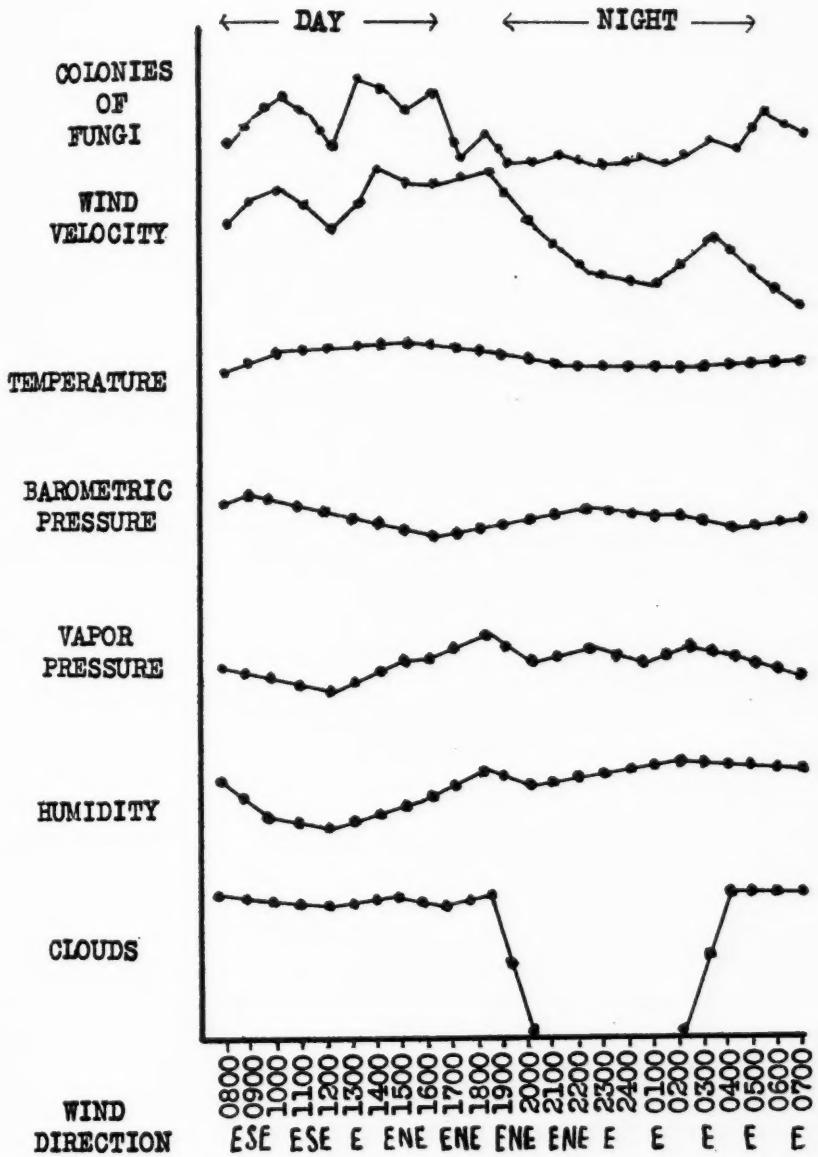
DAY
NIGHT
COLONIES OF FUNGI
WIND VELOCITY
TEMPERATURE
BAROMETRIC PRESSURE
VAPOR PRESSURE
HUMIDITY
CLOUDS
0800 0900 1000 1100 1200 1300 1400 1500 1600 1700 1800 1900 2000 2100 2200 2300 2400 0100 0200 0300 0400 0500 0600 0700
WIND DIRECTION
ESE ESE E ENE ENE ENE ENE E E E E E

Fig. 1.—Comparative graphs of the fungus content of the air, time of day and meterological data. Petri dish exposed to open air for 15 minutes.

dish is quickly put in place on the open dish with the culture medium. This is then incubated at the temperature of the laboratory for three or four days and then the fungus colonies appearing are counted, identified, and studied.

We leave our Petri dish in the interior of the apparatus one hour as in preliminary experiments we observed that at the end of an hour all spores have been deposited from a height of fifty centimeters.

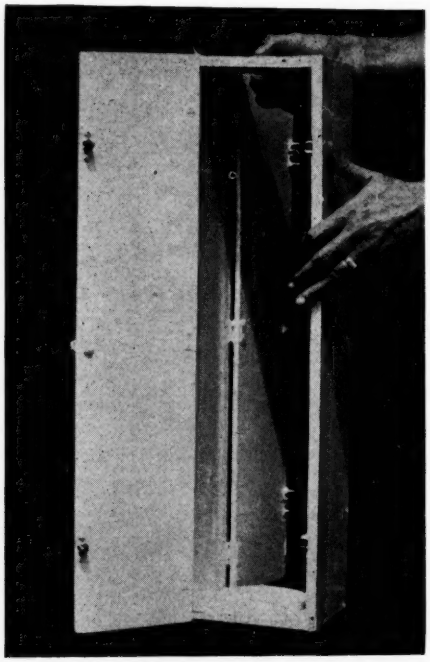

Fig. 2.—Collecting apparatus for the study of air-borne fungi.

In order to determine the volumetric content of fungi, employing Petri dishes with an internal diameter of 9 centimeters, the volume of air which is over the dish will then be $\pi R^2 A$; where R = radius of circle of the culture medium; A = interior height of the apparatus; π = 3.1416. Applying the formula gives a volume of 3816 c.c. of air.

Thus all the colonies cultivated in the Petri dish will be derived from a volume of 3.816 liters of air. To calculate the count of spores or colonies per cubic meter the following calculation applies. $n = \frac{X \times 1000}{3.816}$; n = number of spores per cubic meter; X = number of colonies on Petri dish.

In Fig. 3 is seen the graph which shows the study of the fungi in each of the twenty-four hours of the day, as determined by using this collecting apparatus. It is seen that a curve is obtained whose maximum peak is around 4 A.M. The minimal fungus count is around 6 P.M. It is thus demonstrated that the fungus content of the air of Havana is greater at night than in daylight hours as result which coincides perfectly with our clinical observations.

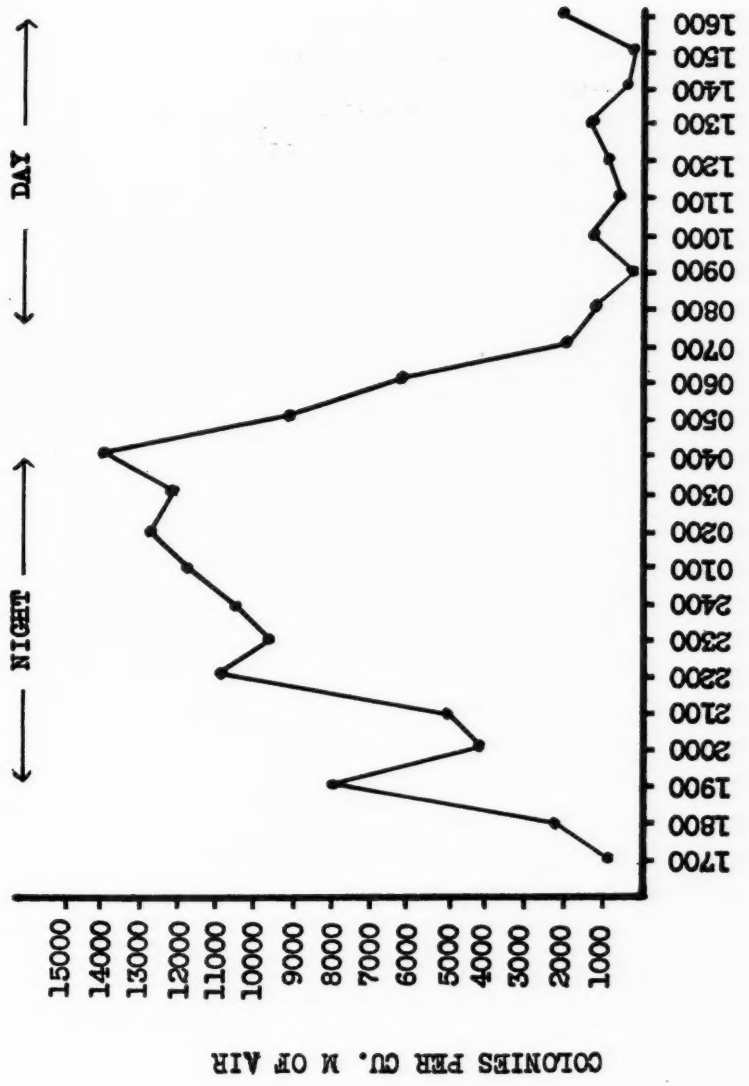

Fig. 3.—Graph of the quantity of fungi of the air every hour of the day. Petri dishes exposed in the collecting apparatus described in the text.

CONCLUSIONS

From serial studies of the fungi of the air of Havana, we conclude that the number of colonies or spores deposited on Petri dishes exposed openly and freely to the air increases on days of increased wind velocity, but this does not mean that the actual number of fungi in a fixed volume of air is greater. The air is the vector of the spread of spores, but nothing else. Hypersensitive cases are worse the days of much wind, but they also become worse when the actual quantity of fungi in the air is high even when there is no wind as happens on many of the nights in our climate. In Havana, this quantity of fungi in stationary air is greater at night than during the day, the graph curve beginning to rise after 6 P.M.

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CONTRIBUTION TO THE STUDY OF THE RETICULO ENDOTHELIAL ORIGIN OF DUST CELLS OR ALVEOLAR MACROPHAGI

VI. Some Histochemical Aspects in the Lungs of Normal Guinea Pigs and Others Submitted to Acetylcholine, Histamine, or Anaphylactic Shock, and So-called Experimental Asthma

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IN A former article by some of us,[1] dealing with the subject of the appearance of cells stained red by using pyronine (Unna's method) on the sputum of asthmatics (with or without bronchial infection) the conclusion was reached that, due to this characteristic staining and their morphological character, the majority of these cells were diverse forms of plasmocytes. Also, though in smaller numbers, alveolar macrophagi or dust cells appeared, the cytoplasm of which stained vividly red with the use of pyronine.

Brachet[2] maintained that with the green methyl pyronine stain the timonucleic acid was selectively colored, and that after previous treatment with ribonuclease and then staining by the former method, did not bring about the red staining of the ribonucleic acid, as this had been destroyed by the ribonuclease. By this means a method for determining the ribonucleic acid was obtained. Nevertheless, in a later article[3] he admits that although the methyl green is chosen for the timonucleic acid, the pyronine, on the other hand, stains not only the ribonucleic acid, but also other basophilic substances such as some glucoproteins.

According to Brachet,[3] Caspersson and Schultz,[4] and Thorell,[5] cells rich in ribonucleic acid cause synthesis of proteins, which is showed by the intense basophilia of their cytoplasm, and this synthesis of proteins in turn, is associated with other biological phenomena such as, hyperglobulinemia[6, 7] and with the increase in the amount of antibodies and gamma globulins.[8-12] Working on this basis, a method was devised for staining the lungs of normal guinea pigs and others which had been subjected to different kinds of shock. The object was to find out if the alveolar macrophagi of these animals fixed the pyronine in the same way as the macrophagi of the sputum from the asthmatics, and also to define whether this positive reaction was due to the ribonucleic acid, which might indicate an intense synthesis of cytoplasmic proteins. In the affirmative case, these cells probably intervene in the hypersensitivity phenomena, showing in this way, the probability of their origin being reticuloendothelial.

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TABLE I. PYRONINE-POSITIVE CELLS

ANIMAL NO.	SUBSTANCE USED AND ROUTE	INTENSITY OF SHOCK	PULMONARY PARENCHYMA						BRONCHIAL MUCOSA		
			NORMAL ZONES		INFILTRATED ZONES		NODULAR ZONES				
			PLASMOCYTES (%)	RED MACROPHAGI (%)	PLASMOCYTES (%)	RED MACROPHAGI (%)	PLASMOCYTES (%)	RED MACROPHAGI (%)	PLASMOCYTES IN MUCOSA	PLASMOCYTES IN SUBMUCOSA	RED EPITHELIAL CELLS
9	Sprayed album.	+	+	+	++	++	++	++	+	+	++
8	Sprayed album. trypan blue	+	+	++	+++	+++	++++	++++	+	+	++
12	Sprayed and sprayed album. shock	+	++	+	++	++	+++	+++	+	+	++
20	Sprayed air	+	+	+	++	+	+++	++	+	+	++
21	Sprayed physiological serum	+	+	+	+	+	++	+	+	+	++
23	Control		+	+	+++	+++	+++	+++	+	+	+++
24	Control		+	+	+	+	++	+	+	+	++
1	Sprayed trypan blue	+	+	+	+	+++	+	++++	+	+	++
19	Sprayed trypan blue	+	+	++	++	+++	++	++++	+	+	++
2	Shock. Sprayed acetylcholine	+++++	++	++	+	+++	++	+++	+	+	++
18	Shock. Sprayed acetylcholine	+++++	+	++	++	++	++	++++	+	+	+++
7	Shock. Sprayed histamine	+++++	+	++	+++	++	+++	+++	+	+	++
17	Shock. Sprayed histamine	++++++	+	++	++	++	++++	+++	+	+	+++
3	Sprayed horse dandruff. Intravenous shock	++++++	+	++	+++	++++++	++++	++++	+	+	++
10	Sprayed album. Intravenous album. shock	++++	+	++	++	+++	+++	+++	+	+	+++
13	Intra-periton. album. Sprayed album. shock	++++++	++	++	+++	+++	+++++	++++	+	+	+++
5	Sprayed album. Sprayed album. shock	+	+	++	++	+++	+++	+++	+	+	++
14	Sprayed album. Sprayed album. shock	++	++	++	+++	+++	++++	++++	+	+	+++
16	Sprayed album. Sprayed album. shock	++	++	++	+++	++++	++++	+++++	+	+	+++
4	Sprayed album. Sprayed album. shock	+++	++	++	++++	++++	+++++	+++++	+	+	++
6	Sprayed album. Sprayed album. shock	+++	+++	+++	++++	++++	++++	+++++	+	+	++
15	Sprayed album. Sprayed album. shock	+++	++	++	++++	++++	+++++	+++++	+	+	++

MATERIAL AND METHODS

Twenty-two guinea pigs were studied; 13 were used as controls and 9 were submitted to different kinds of shock. Of the controls, 2 were not treated at all, so that their lungs could be used for comparison purposes. One was subjected to air pressure under a glass bell. Another was sprayed with pH 8,8 saline solution. Two were sprayed with solutions of 10 per cent egg albumin without trypan blue, and, so as to make the alveolar macrophagi and their originating cells more pronounced, 2 guinea pigs were sprayed with trypan blue according to the technique described in the second article of this series.[13] All the animals which were submitted to shock were sprayed with trypan blue. Later, and at varying periods, the following were submitted to shock: 2 sprayed with acetylcholine at 0.5 Gm. per cent; 2 with histamine at 0.05 Gm. per cent; 1 was sensitized by spraying it with dandruff from a horse and submitted to intravenous shock with the same (10,000 Stull-Cooke units per ml.); another was sprayed with aerosols of 10% egg albumin (1.8 Stull-Cooke units per ml.) and submitted to intravenous shock with the same substance; another was given an intraperitoneal injection of the 10% solution of albumin for 7 consecutive days and submitted to shock by being sprayed with the same solution. Finally the remaining 6 were sensitized by sprays of egg albumin and shocked by treating them 15 days later with aerosols. At the end all were killed by cranial trauma or inhalation of ether. In all these experiments, techniques which have been described in previous papers of this series, were used.[13, 14]

The pathological study was carried out by means of fixation in formol, inclusion in paraffin, section at 5 to 8 μ and staining with eosin hematoxylin; with metaniline yellow[13] for localizing topographically the cells stained by trypan blue; with methylated green pyronine according to Romeis' technique[15]; by the extraction of the perchloric acid according to Pearse's[16] description of the Erikson, Sax, and Ogur technique; with toluidine blue 1:800 for studying the metachromasia according to Hess and Hollander's method[17]; and with the periodic leukofuchsine acid technique according to McManus and Cason's[18] technique for polysaccharides.

Furthermore, lung smears were obtained and stained by Unna's method and also by the May Grunüwald-Giemsa method to distinguish more accurately the cytological characteristics of each of the cells under consideration.

RESULTS

In Table I is shown the distribution of the pyronine-positive cells in the pulmonary parenchyma (Fig. 1) and the bronchial mucosa (Fig. 2) of the different controls and animals submitted to shock. In the pulmonary parenchyma these positive cells are distributed in the normal and abnormal zones, presenting cellular infiltrations which, when merged, cause nodular formations. These positive cells are classified in the first column as plasmocytes, and in the second as histiocytes and "red macrophagi" (red stained by pyronine). According to their number they are classified as + (very few), ++ (few), +++

(regular amount), ++++ (abundant) and +++++ (great abundance). For this the pyronine-positive elements were counted in 10 pulmonary sections of each animal, and the resulting average number was calculated. As for the bronchial mucosa, in the first 2 columns the presence of plasmocytes in the mucosa and submucosa of the bronchi is noted; in the third column the epithelial cells of the bronchial mucosa which showed red stain, are shown; the same system of pluses being used in the diagram as that described for the pulmonary parenchyma.

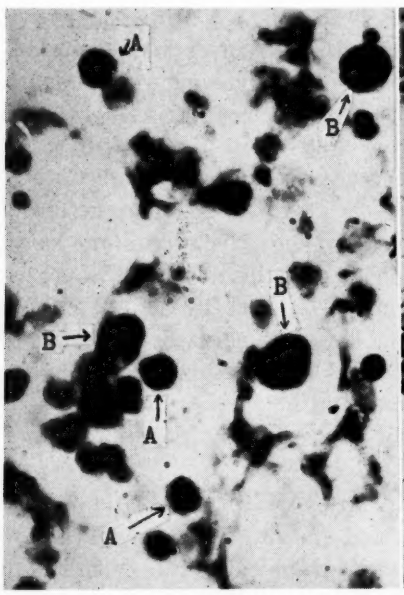

Fig. 1.

Fig. 2.

Fig. 1.—View of pulmonary parenchyma showing plasma cells (*A*) and red macrophagi (*B*), stained red by pyronine.

Fig. 2.—Medium size bronchus showing the epithelial cells stained red by pyronine.

As can be seen, the number of plasmocytes, histiocytes and "red macrophagi" increase as follows: (1) when compared with normal zones, in the infiltrative and nodular zones; (2) in the animals submitted to shock with egg albumin, there was, at times, an appreciable increase in these elements. A smaller number was found in the animals submitted to shock with acetylcholine or histamine; (3) a slight increase in "red macrophagi" appeared in the animals sprayed with trypan blue.

To determine whether the red color of the "pyronine-positive cells" was due to ribonucleic acid, or other cellular components, the groups of animals mentioned in Table II, were compared using the following techniques: green methyl pyronine; the extraction of ribonucleic acid by perchloric acid; and, later, stained by the same procedure with the metachromatic colorants (toluidine blue) and with the PAS technique (periodic-leukofuchsine acid).

The plasmocytes and macrophagi of the pulmonary parenchyma and the epithelial cells of the bronchial mucosa were studied by submitting them to

TABLE II

ANIMAL NO.	SUBSTANCE USED AND ROUTE	INTENSITY OF SHOCK	PYRONINE-METHYL GREEN		EXTRACTION $CLHO_4$		METACHROMASIA		PAS	
			PARENCHYMA PLASMOCYTES HISTIOCYTES	BRONCHIAL MUCOSA CELLS	PULM. PARENCHYMA PLASM.-HIST.	BRONCHIAL MUCOSA CELLS	PULM. PARENCHYMA PLASM.-HIST.	BRONCHIAL MUCOSA CELLS	PULM. PARENCHYMA PLASM.-HIST.	BRONCHIAL MUCOSA CELLS
23	Control	–	+++	+++	–	–	–	+	–	++
24	Control	–	+	++	–	–	–	+	–	++
20	Air	+	++	++	–	–	–	++	–	+++
21	Sprayed physiol. serum	+	+	++	–	–	–	++	–	+++
9	Sprayed album.	+	++	++	–	–	–	+	–	++
8	Sprayed album. trypan blue	+	+++	++	–	–	–	++	–	+++
12	Spray and album. shock	+	++	++	–	–	–	+	–	++
1	Sprayed trypan blue	+	++	++	–	–	–	++	–	++
19	Sprayed trypan blue	+	++	++	–	–	–	+	–	+++
2	Spray-shock acetylcholine	+++++	++	++	–	–	–	++	–	+++
18	Spray-shock acetylcholine	+++++	++	++	–	–	–	++	–	+++
7	Spray-shock histamine	+++++	+++	++	–	–	–	+++	–	+++
17	Spray-shock histamine	+++++	++	+++	–	–	–	+++	–	++++
3	Sprayed horse dandruff. Intravenous shock	++++++	++++	++	–	–	–	+	–	+++
10	Sprayed album. intra-periton. Intraven. shock	++++	+++	+++	–	–	–	++	–	+++
13	Intra-periton. album. Shock sprayed album.	+++++	++++	+++	–	–	–	+++	–	++++
5	Sprayed album. shock. Sprayed album.	+	++	++	–	–	–	++	–	++
14	Sprayed album. Sprayed album. shock	++	++++	+++	–	–	–	++	–	++++
16	Sprayed album. Sprayed album. shock	++	++++	+++	–	–	–	+	–	+++
4	Sprayed album. Sprayed album. shock	+++	++++	++	–	–	–	+	–	+++
6	Sprayed album. Sprayed album. shock	+++	++++	++	–	–	–	+	–	+++
15	Sprayed album. Sprayed album. shock	+++	++++	++	–	–	–	+++	–	++++

each one of these tests. All the positive elements found in 10 pulmonary zones, for each one of the techniques used, is shown together with the corresponding average, using the same system of estimation as that described for Table I.

After using methyl green pyronine, a greater number of positive cells appeared more frequently in the pulmonary parenchyma than in the bronchial mucosa. The number of these "positive cells" increased in nearly all the guinea pigs submitted to shock by albumin, more in the pulmonary parenchyma; that is to say, the number of plasmocytes, histiocytes, and macrophagi stained red by pyronine increased. On the other hand, the number of "positive cells" in the bronchial mucosa was less. With the extraction of the ribonucleic acid by perchloric acid and the subsequent staining by green methyl pyronine, the result was as follows: (a) The cytoplasm of the plasmocytes and the alveolar macrophagi was almost always a pale pink color (Figs. 3 and 4). On rare occasions the pink was deeper. The nucleus of both cellular types, more so in the plasmocyte nucleus, did not remain a greeny-blue, but became a bright pink, (b) The epithelial cells of the bronchial mucosa were not red either, but only a pale pink (Figs. 5 and 6).

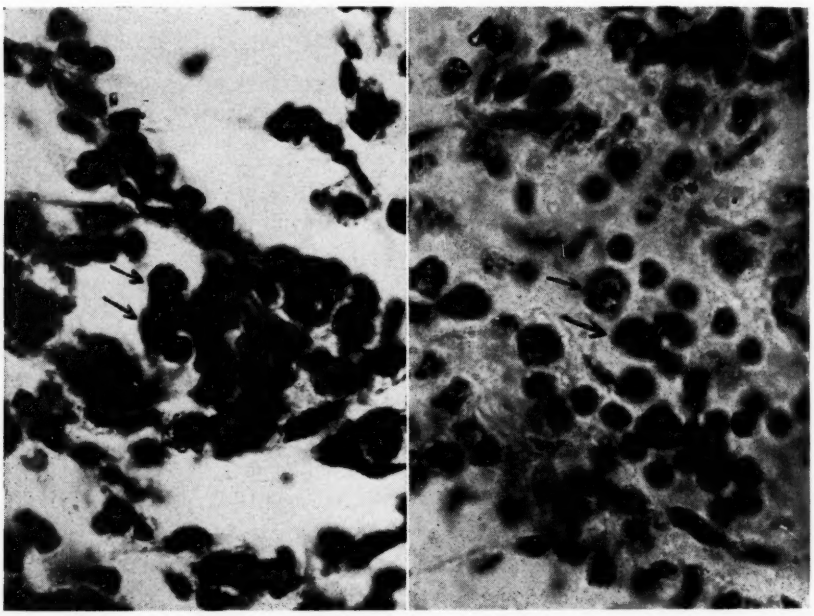

Fig. 3. Fig. 4.

Fig. 3.—View of pulmonary parenchyma showing an infiltration with plasma cells and macrophagi (arrow) stained red by pyronine.

Fig. 4.—The same pulmonary parenchyma immediately before Fig. 3, which were first treated with perchloric acid and then stained with pyronine. Observe the loss of tintorial affinity about pyronine. Arrows indicate macrophagi.

With metachromic (toluidine blue) stain, there was no positive cell in the pulmonary parenchyma: that is to say, metachromic or chromophore. On the contrary, the number of epithelial cells of the bronchial mucosa varied, increasing slightly in those animals submitted to shock.

With PAS (periodic-leukofuchsine acid) no positive results were obtained either in the plasmocytes or the macrophagi of the pulmonary parenchyma. Nevertheless, other positive cells were found which are not included in the

table as they are of a different nature to those under consideration, and correspond to Kurloff's corpuscular cells. Also, in the vascular lesions in those animals submitted to shock, positive reaction was found. (This also is not included in the table for the same reason as has been given previously. This item, together with the aforesaid cells, will be explained in a later article.) On the other hand, a great number of the epithelial cells of the bronchial mucosa were definitely positive, the number increasing moderately in the animals submitted to shock.

The histologic characteristics of all the positive cells with green methyl pyronine, were precisely defined in smears from the lungs of each animal studied, using the same method. A greater predominance of mature plasmocytes over the immature and over the transition forms (according to Fagraeus' classification[10]) was observed. As for the alveolar macrophagi, with red cytoplasm and the inclusion of carbon or trypan blue (or both simultaneously), they predominated over the histiocytes with red protoplasm, in the proportion of 2 to 1 (Fig. 7).

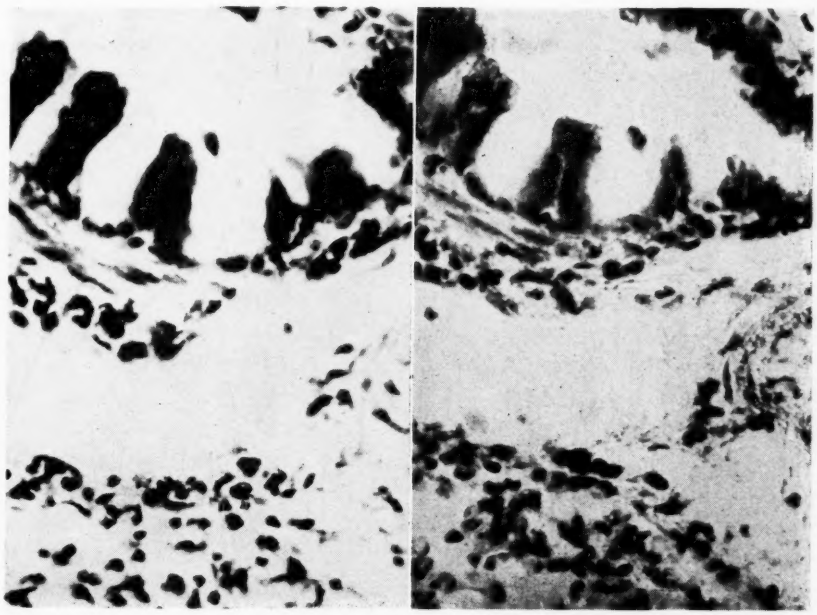

Fig. 5. Fig. 6.

Figs. 5 and 6.—The same broncho-pulmonary view as Fig. 4 showing the difference in color between the bronchial cell directly stained by pyronine (Fig. 5) and that first treated with perchloric acid (Fig. 6).

COMMENT

As can be seen in Table I, a varying number of elements stained red by pyronine, was found in all the animals. These, on the one hand, were interpreted as being diverse forms of plasmocytes, and on the other, as histiocytes and macrophagi situated at the opening and in the lining of the alveolus, interalveolar spaces, around vessels and in those zones of the pulmonary parenchyma which were infiltrated and nodular (Figs. 1 and 3).

The proportion of red macrophagi in relation to the number of macrophagi vitally colored with the trypan blue, varies between 1 per cent and 5 per cent, increasing (as has already been shown in previous papers of this series) in the animals submitted to shock.[14]

Klinge[19] has already described in the state of Aschoff's experimental nodular condition in sensitized animals, the proliferation of great basophil cells which become intensely red colored with the pyronine. This agrees with the results obtained in the animals sensitized with albumin, but it is pointed out that it is not certain that such pyronine positive elements (whether they are plasmocytes, histiocytes or macrophagi) are pathognomics of the hypersensitive state and allergy as Mas and Magro[20] maintain for the plasmocytes. All these cells were present in the controls, although in a smaller number. Also Von Albertini and Grumbach[21] found great quantities of plasmocytes in their experiments on animals with focal streptococcal infections. In the foci of infection with these bacteria, a great number of plasmocytes appeared, it being difficult to prove that their presence was due only to hypersensitivity reactions.

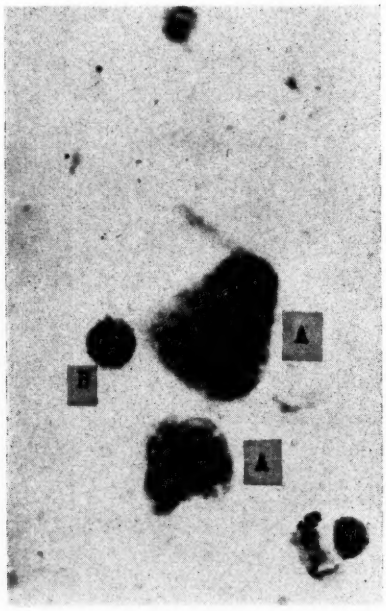

Fig. 7.—Two red macrophagi (*A*) and a mature plasma cell (*B*) stained red by pyronine from a pulmonary smear. (Photomicrograph greatly enlarged.)

In spite of this, it is evident that the plasmocytes as well as the alveolar macrophagi stained red by the pyronine reaction have a high cytoplasmatic content of ribonucleic acid, which in its turn (according to Brachet,[3] Fagraeus,[16] Erich, Drabkin, and Forman,[12] Pearse,[16] and White[22]) brings about intense cellular activity in the protein synthesis.

But, as the red staining by pyronine according to Brachet,[3] can also be caused by some basophilic protoplasmic elements, such as some glucoproteins,

metachromic stains[17] and periodic-leukofuchsine acid (PAS)[18] were resorted to so as to avoid this possibility.

With the first method, an evident metachromasia in the epithelial cells of the bronchial mucosa was obtained, which never appeared in the alveolar macrophagi, although Wislocki, Bunting, Dempsey, and Pearse[16] and Mancini[23] maintain that on occasions the ribonucleic acid can set up a metachromic reaction. It is true that, in some macrophagi, an intense basophilia (which has been already discovered by Kallos and Pagel[24] and Kallos and Kallos[25] in the lungs of animals with experimental asthma) was found.

By this means the mucopolysaccharide acids in the composition of the alveolar macrophagi (whether they are sulfated[26-29] or not[16, 23, 30, 31] can be discounted, as in the latter no metachromic reactions were obtained. On the other hand, this reaction was particularly intense in the epithelial cells of the great and medial bronchi, thereby proving their mucoproteinic contents (see Table II).

The red coloring of the dust cells by the pyronine, due to the nonacid glucoproteins, can also be discounted, as, by using PAS (which gives a positive reaction with glucoproteins, whether they are acid or nonacid,[16, 18, 23, 30-34] none of the above mentioned cells gave a positive reaction. On the contrary, the epithelial cells of the mucosa of the great and medial bronchi, were intensely positive, in the same way as the vascular lesions in the animals submitted to shock and the cells with Kurloff's corpuscles. Pearse[35] with the latter, also obtained positive reactions using the same technique.

Besides, Russell's corpuscles of the plasmocytes, are positive using PAS according to this author, and in those cases the red stain with pyronine becomes less intense because the chemical composition of the protoplasm has been modified by the appearance of the said corpuscles.

Finally, for the extraction of the ribonucleic acid by means of perchloric acid, Pearse's description of Erikson, Sax and Ogur's method[16] was chosen instead of the ribonuclease recommended by Brachet, because Pearse[16] and Lisson[28] maintain that it is difficult to obtain ribonuclease free from impurities. These impurities may contain ferments which might digest other cellular components apart from the ribonucleic acid.

Nevertheless, after the application of the perchloric acid, it was not possible to establish the exact difference between the chemical composition of the pulmonary parenchymal cells (plasmocytes and alveolar macrophagi) and between the epithelial cells of the bronchial mucosa.

In fact, in a series of sections taken from the lungs of the animals studied, and stained respectively, one section with green methyl pyronine, and another with this same method, after the application of 10 per cent perchloric acid at 4° C. during 16 hours, the extraction of the cellular components which stain red with pyronine was achieved, as much in the case of plasmocytes and macrophagi as in the bronchial epithelial cells. The color of all these cells was a pale pink after the application of the perchloric acid.

So that, as by means of the other techniques used, a difference in chemical composition between the plasmocytes and macrophagi on the one hand and between the bronchial epithelial cells on the other was exposed, it must not be

concluded that the perchloric acid is the only method to be chosen for the ribonucleic acid, because it is possible that it destroys this acid and the mucoproteins of the bronchial cells.

Perhaps this is due to the time it was exposed with the perchloric acid, for as Pearse maintains[16] so far this time limit has not been fixed satisfactorily.

In short, (Fig. 7) it can be said that some alveolar macrophagi are rich in ribonucleic acid as shown by their red staining with pyronine, discounting the possibility that this color is produced by glucoproteinic components, whether they are acid or non-acid, because the metachromic and PAS reactions are always negative in these cells. On the other hand these reactions are positive in the epithelial cells of the bronchial mucosa, owing to their mucopolysaccharide contents which also produce a red reaction with pyronine (Figs. 2 and 5). Therefore, there is evidently a difference in the chemical composition of the branchial epithelial cells and of the dust cells, caused by the carrying out of their separate functions, as the first, according to the histochemical reactions, form mucoproteins. Contrarily, the second possess a large quantity of ribonucleic acid, also proved by the histochemical reaction of the cells. This indicates intense protein synthesis (possibly the formation of antibodies) which, together with their other properties (macrophagi, vital coloring with vital dyes and active mobilization, already studied in other articles of this series[13-14]) makes the reticuloendothelial origin of the alveolar macrophagi probable.

Nevertheless, the intervention of other cellular elements is not to be discounted in the formation of antibodies, such as that already mentioned in the plasmocytes and even in the lymphocytes, which, according to Harris and Harris[37] are also stained red by pyronine.

CONCLUSIONS

1. In the pulmonary parenchyma of guinea pigs (to the same extent in the controls as in those submitted to different shocks) cells appeared which were stained red by pyronine and which were considered to be plasmocytes, histiocytes and alveolar macrophagi.

2. This red coloring with pyronine was due to the large quantity of ribonucleic acid.

3. The possibility of this red coloring with pyronine being due to the presence of acid or nonacid glucoproteins was discounted as the metachromic and PAS reactions were negative in the cells which gave a positive reaction with pyronine.

4. A net result for the extraction of ribonucleic acid by the application of the perchloric acid was not obtained, because it extracted the contents from the cells containing this acid just as much as the contents from the cells rich in mucoproteins.

5. It was considered that the said alveolar macrophagi, owing to their rich contents of ribonucleic acid (as proved by their staining red with the pyronine) and by their moderate increase in the animals submitted to shock with albumin, took an active part in the allergic phenomena.

SUMMARY

The alveolar macrophagi or dust cells from the lungs of control guinea pigs and others submitted to different kinds of shocks, were studied, using histochemical techniques as the green methyl pyronine, extraction of ribonucleic acid by perchloric acid, metachromatic reactions, and the periodic-leukofuchsine acid reaction. It was shown that the said cells were positive only when the green methyl pyronine method was used, thereby proving a high cytoplasmic content of ribonucleic acid.

As these red alveolar macrophagi increased slightly in the animals submitted to shock, in the same way as other elements of the reticular endothelial system which take part in the formation of antibodies, they can probably be considered as of the same origin.

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BRONCHIAL ASTHMA DUE TO RAT AND MOUSE HAIR

Report of Two Cases

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SENSITIVITY to the dander of animals is well known, and sensitivity to the epithelia of rodents has been recorded in the literature[3] since 1897, when Gould and Pyle[1] reported that "many people are not able to endure the emanations from cats, rats, mice, etc." Lintz[2] in 1923 reported the case of a woman whose asthma occurred only in her residence. Her home was infested with rodents and when these were eradicated she became symptom-free. She was not skin tested, but exposure to a mouse promptly precipitated an attack. Rodent infestation of homes and factories is certainly not unusual, and if considered by the physician, may explain some elusive problems. The two following cases are, therefore, presented.

CASE REPORTS

Case 1.—Mrs. L. F., a 23-year-old white housewife, was first seen in the Allergy Clinic of the Rhode Island Hospital in May, 1940. Her history began in August of 1937, with a sudden attack of asthma which persisted until November. After that the attacks were intermittent and mainly in the winter months. There were a dog, a cat, and a canary at home and she was worse when in contact with dust. The family history was positive, her father having asthma. The positive findings of the physical examination were limited to the chest where expiratory musical râles were heard throughout both lung fields. An x-ray of the chest was normal. Skin testing revealed 3+ positive reactions to cat, feathers and dust.

The Clinic nurse made a home visit and reported finding a neat, orderly, clean home in one of the poorer districts of Providence. She instructed the patient in dust precautions. The patient was seen three times in the next month, receiving small doses of house dust by injection and potassium iodide by mouth. She reported improvement and disappeared from the Clinic.

In August, 1949, she again appeared with the story that shortly after her last visit she had moved to another neighborhood where she had had absolute freedom of asthma for eight years. The same animals and furniture were present in this new location. In November of 1948, she moved back to the neighborhood where she had previously lived, and sneezing and nasal blockage recurred almost immediately. By April, 1949, she was once more having asthma and its recurrence finally forced her return to the Clinic.

The physical findings at that time were the same as before, asthmatic râles being noted. Thorough questioning revealed that her present residence and that first lived in were infested with mice and that the home in a better neighborhood was free of these rodents. Scratch tests were repeated an a 1+ reaction was obtained to feathers and dust, and a 2+ reaction to mouse dander and dust from her home. Rhinorrhea and nasal itching came on during the testing and persisted for two hours.

As a result of this finding, the patient made an energetic attempt to eliminate the rodents and improvement occurred. In the spring of 1950 she moved again to a house in the neighborhood where she had previously been free of symptoms. The same furniture was taken with her. Immediate relief occurred.

In the summer of 1951, upon returning from a vacation, asthma once more recurred. It became persistent and severe necessitating adrenalin for relief. Evidence of mice was noted and a mouse was actually trapped. Once again the rodents were eliminated by trapping and the patient was given small doses of mouse dander. After three weekly injections, she was symptom-free and has remained so since.

CASE 2.—F. M., a single 28-year-old machinist was seen in the office in August, 1951, with a history of asthma beginning four years previously. The family history and past history were negative for allergy. The symptoms came on after working in a factory for eighteen months and only occurred at work. He moved to another factory with no relief. He then quit work, set up some machines in his own cellar, and for the next two years performed the same work with no difficulty whatsoever. He then went to work in a third factory and after two or three months again noted the onset of asthma. The symptoms occurred almost immediately after getting to work and disappeared on the way home. He never had asthma in any other place. In his employment he handled steel, brass, and oils. There were no lacquers or ordinary antigenic materials. Careful questioning revealed that the factories, all located near the wholesale fruit and meat markets, were heavily infested with rats.

The physical examination showed no abnormality. Intracutaneous skin testing with the routine dusts and danders was negative, but a 3+ positive reaction to mouse dander and a 4+ positive to rat dander were obtained. Passive tranfer testing merely corroborated the results of direct testing.

Treatment with mouse and rat dander was begun in September. Local reactions were obtained and the dosage increase had to be small. By November of 1951 the patient was able to work in the factory with no difficulty except for slight symptoms on Monday mornings after the shop had been closed over the week end.

SUMMARY

Two cases of asthma due to the dander of rodents are presented.

Sensitivity to rodents may be more common than previously supposed, and questioning regarding infestation of the patient's environment should be made routinely.

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Editorial

TRADITIONALLY asthma is a disease causing prolonged and recurrent disability but not death. This belief, based on innumerable rapid recoveries from what appeared to be imminent asphyxia, gained support from the studies of Matthew Walzer who, in 1931, after a careful search of the literature, was able to collect only 33 autopsied cases in which the reports were sufficiently complete to be of value. Such an optimistic view encourages constant therapeutic efforts in desperate cases but should not lead to the blind trust that the outcome of asthma will always be favorable. This is strikingly illustrated by the article of Dr. Stearns S. Bullen published in this issue, which reviews the deaths of 176 patients with asthma, 94 of whom died during asthmatic attacks, all treated in three hospitals. Autopsies performed in a large proportion of the cases showed a variety of contributing causes of death, but many of these, especially lesions of the heart and lungs, may well have resulted from the prolonged strain of asthma. It is apparent that uncontrolled asthma may be a real threat to the life of the patient and that further studies of the actual mechanisms of death are important.

Many physicians of wide experience in the field have expressed the opinion that death from asthma is the result of mistreatment or even of the medication used rather than the disease itself. For example, a recent textbook states that "death in uncomplicated asthma is rare unless morphine has been used." However, in the series reported by Dr. Bullen, morphine was used only sparingly and could be considered a contributory cause of death in only a few cases. Since all were treated in three large university hospitals, the patients he describes may be presumed to have received therapy as good as is generally available elsewhere.

In considering fatalities from asthma, it is at once apparent that the prognosis is very different in asthma due to demonstrable external allergens and in so-called "intrinsic" asthma. Patients of the former type usually develop symptoms early in life and frequently live to a ripe old age despite recurrent attacks. Their survival may be due in part to the therapeutic efforts of the allergist, but even if these methods are neglected, the change of environment on admission to a hospital is often beneficial. Patients with "intrinsic" asthma, possibly resulting from infection, are more apt to develop symptoms in middle age and may succumb within 10 years. It is this group who present a real therapeutic problem at present.

In the autopsy studies of patients whose deaths were apparently primarily due to asthma, as in the smaller group reported by I. Walzer and Frost, the outstanding finding was extensive plugging of the bronchi by tenacious mucus. It is recognized that mucosal edema and spasm of the bronchial musculature,

which are usually presumed to play a part in the occurrence of asthma, are often difficult to demonstrate after death, but the importance of the thick and excessive secretions cannot be disregarded in the treatment of status asthmaticus. The wide distribution of such plugs in the smaller bronchi of the bronchial tree in most instances casts doubt on the possibility of efficacious relief by bronchoscopic aspiration. While iodides and bronchodilating drugs may be helpful, much depends on the ability of the patient to dislodge the secretions by coughing; care must be taken that the cough reflex is not unduly suppressed by sedatives in critically ill patients.

Since either chronic or acute infection plays an important part in the causation of many of these cases of intractable asthma, full use should be made of the available antibiotics. When possible, the suitability of the drugs used should be checked by bacteriologic cultures of the sputum and tests of bacterial sensitivity.

Most if not all of the deaths reported by Bullen occurred before the introduction of cortisone and corticotropin in the treatment of asthma. It remains to be seen how effective these drugs will be in reducing the death rate from asthma. However, their proved efficacy in status asthmaticus and the accumulating evidence that oral cortisone may be used over long periods by patients with severe chronic asthma suggests that they may be a real factor in prolonging life. While they should ordinarily be reserved for those patients in which attempts to treat the cause of the asthma, and also therapeutic trials of the simpler means for symptomatic relief, have failed, they should not be withheld until the situation is hopeless.

W. B. S.

American Academy of Allergists

PRESIDENT'S ADDRESS

A FEW days ago I read in one of the New York papers a statement to the effect that 500,000 people in New York City are suffering from diseases of the heart and blood vessels and, in 1950, 78,922 New Yorkers died of them. Then further in the same article it indicated a fund goal of $1,100,000 to carry on a national and community crusade to finance medical research and better facilities for the care of the patient in the field of cardiovascular disease.

When it comes to the allergic diseases, the general public fails to grasp the serious significance of hay fever, bronchial asthma, and eczema as causes of chronic disease and disability, nor has the general public much idea of the broader concepts of allergy and its relation to drug reactions, the various manifestation of collagen disease, and bacterial infection. To many lay people, "allergy" is the rash you get when you eat strawberries. Among many physicians exposed to very little instruction in medical schools, usually to only an occasional asthmatic on the hospital ward during their internship, patients with allergic diseases are often regarded as medical bores to be treated with tolerance and, as soon as possible, advised to seek some different climate and a different doctor. Even among allergists, I doubt that there is sufficient awareness of the great part that the allergic diseases play in the magnitude of the chronic disease problem here in the United States. Here are some figures: 3,900,000 individuals in the United States in 1948 suffered from hay fever and asthma. This estimate by the United States Public Health Service ranks the prevalence of these diseases third in a tabulation of chronic disease, following diseases of the heart and circulation which lead the list, and arthritis and rheumatism which are second.

In the United States, 9,000 persons with bronchial asthma die each year and, in the year of 1940, asthma was the primary cause of death in 2,233 cases. These figures are cited by Dr. Louis I. Dublin and Mr. Herbert H. Marks, statisticians for the Metropolitan Life Insurance Company.

In World War I, 7,797 patients with bronchial asthma were admitted to Army hospitals, approximately 2 in every 1,000 or almost three times the number admitted for peptic ulcer. Over 30 years later, 3,318 veterans of that war whose asthma was service-connected were on the compensation rolls; 4,806 others became totally incapacitated from the disease in the interim and received pensions. In 1944, at the time the U. S. Navy was at its peak enrollment, there were 6,932 cases of bronchial asthma accounting for 470,090 sick days during that year. As of June 30, 1950, 36,541 veterans of World War II (all services) were on compensation rolls for asthma.

Turning aside from statistics it should be better recognized among laymen and physicians that hay fever often leads to bronchial asthma, chronic nasal polyposis, and sinus disease; that all bronchial asthma in infancy is not a harmless affliction that is outgrown, but may often lead to chronic adult asthma and even death from cardiac-pulmonary disease in middle adult life; that bronchial asthma, unless the causes are removed, may progress likewise to pulmonary emphysema, pulmonary fibrosis, and cardiac failure.

While statistics are not so readily available for the allergic skin diseases, I do not need to emphasize to this audience the tragic discomfort of the infant and young adult with eczema, nor the numerous manifestations of skin disease of the atopic and contact type in adult life. We are all aware too, of the problem of hypersensitivity to drugs now becoming increasingly urgent with the use of the antibiotics and the hazard, as time goes on, of more individuals becoming sensitized.

It is obvious that the allergic diseases present a challenge to medical education to train physicians able to cope with the problems. From the standpoint of education in the allergic diseases at the undergraduate level, to quote from Swineford, instruction in our medical schools is haphazard and inadequate in most places where given and, in some medical schools, is neglected entirely. From the standpoint of medical internship, very few institutions provide for any rotation through the allergy clinic or any real experience and training in the treatment and diagnosis of the allergic disease. When it comes to the training of residents and fellows in allergy there are just 13 institutions in the United States approved by the Council on Medical Education for this purpose and the majority have difficulty in obtaining high grade men to avail themselves of these opportunities.

Finally, there are 181 men in the United States certified in Internal Medicine or Pediatrics plus allergy. These individuals are limited to 30 states and the District of Columbia. There are 18 states without an allergist who is certified in allergy. As for Academy Fellows, 14 states are without an allergist of this rank.

I have tried to paint a realistic picture of the seriousness and the wide prevalence of the allergic diseases in this country, and at the same time to indicate the failure of medical education to train enough physicians capable of adequately treating the sufferers from this group of diseases. What is the solution? The answer probably lies in a strong aggressive Foundation for the Allergic Diseases set up with the purpose of better education of the public and physicians in the importance of the allergic diseases and what constitutes good diagnosis and treatment. Such a foundation, in addition to its educational function, should be organized to raise money for better care of patients with these diseases, to finance investigation and research, and to subsidize the training of men well qualified to treat these diseases through residencies and fellowships.

Last year the Academy approved the form of organization of the Foundation for the Allergic Diseases. Today we activate it by electing medical trustees at large. During the coming year, it is to be hoped that an active group of lay trustees will be persuaded to lend their support to this effort. There is no reason

why this Foundation should not function as well in its field as the American Cancer Society, the American Heart Association, and the Arthritis and Rheumatism Foundation do in theirs. The challenge is here. As allergists interested in the better development of our field, and conscious of our obligation to the many sufferers from allergic disease, we must get behind the Foundation and make it a constructive force in American medicine.

So much for this. In our ambitions for the future we must not forget the accomplishments of the past.

First, I should like to mention the organization of the International Association of Allergology at Zurich last September. By vote of the Fellows the Academy participated in the organization and pledged itself to join with the American College of Allergists and 30 foreign allergy societies to carry on, in an international way, free interchange of information and ideas and to advance progress in this field. The Acadmey owes a debt of gratitude to Dr. Fred Wittich, one of its Fellows and also Secretary of the College of Allergists, who has done so much to found this organization, and to Dr. Howard Osgood and other members of the Academy's Committee on International Relations who worked so carefully and so hard for this great accomplishment. Mention of the international aspects of allergy would not be complete without reference to the meeting of the First International Congress on Allergy held also in Zurich last September in which a number of members of the Academy attended and participated.

In our own country it has been gratifying during the past year to note the appreciation expressed by the Surgeon-Generals of the Army, Navy, and Air Forces and the Chief Medical officer of the Selective Service System in reference to the report of the Academy Committee on Standards for Induction of Draftees into the Armed Forces. Surgeon-General Pugh of the Navy followed this up with a request for an opinion of the Academy as to the importance to be attached to a history of asthma in candidates for officer training. All Fellows of the Academy were polled in this important question and the results sent to him. The Food and Drug Administration, through Acting Medical Director Dr. Irving Kerlan, asked for a joint Committee of the Academy and College for purposes of consultation. This request has been complied with. Dr. Leo Criep is the Chairman of this Committee.

The educational efforts of the Academy are for the most part centered in the activities of the Committee on Education, the Annual Scientific meeting, and THE JOURNAL OF ALLERGY. The Committee on Education has been most active in its subdivision of Postgraduate Education. A successful seminar was held at Montreal under the direction of Dr. Bram Rose. Early in the year a postgraduate program in connection with the annual meeting was proposed. After consideration it was approved by Dr. John Sheldon, Chairman of the Committee on Education, and Dr. Max Samter, Chairman of the Sub-committee on Post Graduate Education, went to work. The results of his labor you are all familiar with. I feel much indebted to Dr. Samter for the inauguration of this program during my administration. He has set a high standard which undoubtedly will remain as an ideal for years to come.

The Scientific Program has, I believe, been most interesting and constructive. There were 51 papers submitted. This speaks well for the spirit of active investigation and research that prevails in our membership. THE JOURNAL OF ALLERGY has had a good year. The articles are of high standard scientifically, and their practical clinical side is not to be neglected. Dr. Sherman and his Board have conducted a more active editorial policy than in the past, and this seems desirable. The JOURNAL is a part of the Academy—it be'ongs to its Fellows and Members. Constructive criticism from Fellows and Members relative to the JOURNAL is always welcome.

The Research Council continues its efforts under great handicaps. Dr. Walzer will report later at the meeting. With the formation of the Section on Foods, the Coordinating Board of the Research Council becomes activated. It is to be hoped that as the Foundation on Allergic Diseases prospers more funds will be available for the research projects of the Research Council. At present its operations are greatly handicapped by lack of financial support.

The Executive Office with Mr. James O. Kelley as Executive Secretary and Mr. Al Luthmers as Assistant Executive Secretary continues to be invaluable to the Academy. The arrangements for the annual meeting and the selling of space for commercial exhibits are most important. The Biennial Directory which appeared this year is entirely the work of the Executive Office. During the past year the necessity for stricter budgeting of annual expenses has been urgently stressed by Mr. Kelley, and the Budget Committee, consisting of the Secretary, Treasurer and Chairman of the Committee on Education, has taken its responsibilities seriously in the matter of anticipating the annual expenses and receipts of the Academy.

At this time I want to pay my tribute to Dr. Ben Rappaport and the members of the Local Committee on Arrangements for the preparations they have made for our comfort and entertainment, and especially to the Hostess Committee. With Mrs. Rappaport as Chairman, the members of this committee have given our wives a most enjoyable time. It has been a friendly, cordial occasion which we shall long remember. Last, I want to thank the Schering Corporation for their generous and pleasant cocktail party which we enjoyed last evening.

May I state that it has been my good fortune to meet groups of allergists in the South at St. Petersburg, in the Southwest at San Antonio, and the Midwest in Detroit. As an easterner I am greatly impressed with the national character of our organization and the friendly spirit one encounters as a visiting allergist. As one travels over the country and meets various members of our specialty one does not find agreement on every phase of the practice of allergy, but I have been greatly impressed with the sincerity of the men in our field, their enthusiasm, and the very earnest effort they are doing each in his own way to practice allergy honestly and to the best advantage of the sick patient. It has been a great honor to have been the President of this Academy and I thank you.

The problems of the Academy are numerous and complex. As a national organization with a large membership from all over the country, there are diverse interests which not infrequently clash. The existence of two national

allergy societies, naturally to some extent rivals, increases the difficulty. But the fact that we are a large national organization increases our potential strength, and two national societies working together on projects which are for the food of our mutual field may enhance the efforts of each.

When I assumed the presidency last year, I stated my hope that during my term the efforts of allergists in this country might be better unified toward the solution of the problems which face us. I believe we have made progress.

In closing may I express my sincere gratitude to the members of the Executive Committee, the various Chairmen and members of Committees, and to our Executive Secretaries who have labored to do a good job during the year that now closes.

The years ahead bring new leaders and new problems. I am reminded of a little prayer that was recently made by the Chaplain of the United States Senate in opening one of the sessions of Congress. The chaplain is reported to have said,

"Lord, protect us from hot heads that would lead us to make foolish decisions and from having cold feet that would lead us to do nothing at all."

Dr. Hooker Resigns From Editorial Board

The Editorial Board regrets to announce the resignation of Dr. Sanford B. Hooker of Boston, who for many years has served as a valuable Editor and adviser in connection with immunological aspects of allergic diseases. He is being replaced by Dr. Elvin A. Kabat of Columbia University, New York City, who brings an extensive background in experimental immunochemistry which will be most helpful to the editorial board.

HISTORIAN'S REPORT

THE Eighth Annual Meeting of the Academy was held on February 18, 19, and 20, 1952, at the Hotel Sherman in Chicago, Ill. The weather was mild, with some sunshine and practically no snow. The total registration was 503, not including wives and families: 389 members and guests, and 114 exhibitors.

Thirty-five commercial exhibits were set up and these were very well attended. Four scientific exhibits were placed at the rear of the assembly room, a convenient arrangement for study.

The Pollen Survey Committee, under the chairmanship of Mr. O. C. Durham, displayed the work of 1951 and previous years. This survey now extends over the whole North American continent including Mexico. All forty-eight of the United States and the District of Columbia are included, as well as Alaska. In Canada, nine provinces are represented from Alberta to Newfoundland; British Columbia, the Yukon, and the most northerly areas are absent. Bermuda, Cuba, and the Virgin Islands have been reported. In a table giving the ragweed pollen index, covering past years and revised to date, there were listed 424 pollen-counting stations in the United States, eighty-three in Canada, three in Mexico, and three outside the continental area, a total of 513 stations recorded. The pollen counts in 1951 were made by over eighty committee members. To this number should be added the National Park Services of the United States and of Canada, the United States and Canadian Weather Bureaus, and a number of State and local health departments. Few of us realize the monumental amount of work this committee has accomplished, and how much American allergy owes to its members. Besides Mr. Durham, Chairman, the central pollen committee is composed of A. Orville Dahl, Ph.D., Chairman of the Department of Botany, University of Minnesota, Dr. Theodore L. Squier, and Dr. Matthew Walzer.

Two other committees of the Academy, the Mold Survey Committee with Dr. Leonard Harris as chairman, and the Herbarium Committee with Mr. Durham as chairman, presented modern exhibits of their results. Space does not permit at this time a detailed discussion of their extensive work. The excellent exhibit of Dr. Joseph Fries of Brooklyn showed, among other things, roentgenographic changes in the gastrointestinal tract of reactions to food sensitivity in children.

Numerous committee meetings were held at the Hotel Sherman during the three days preceding the opening of the scientific sessions, and many of these meetings were continued at intervals during the succeeding days.

Under the general chairmanship of Dr. Max Samter, three highly instructive postgraduate courses were held at the Sherman Hotel on February 15, 16, and 17: Techniques of Experimental Immunology as Applied to Allergy, A Visiting Allergy Clinic, and a Course on Dermatologic Allergy. Coincidentally, a 3-day course on the Identification and Biology of Fungi and Pollen was given

on the Chicago Campus of Northwestern University Medical School. These courses were attended to capacity, so much so that at times the previously reserved meeting places were unexpectedly overcrowded. Dr. Samter and the "faculties" are to be congratulated on the high quality of the discussions.

Mrs. Ben Z. Rappaport and the members of her Hostess Committee had planned interesting entertainment for the visiting ladies, including luncheons at Marshall Field's and at Henricis'. The Chicago Allergy Society served tea each afternoon and the Schering Corporation entertained at cocktails late Monday.

The scientific assembly began Monday morning, with an opening attendance of about 225, which rapidly increased. The sessions from Monday until Wednesday noon were uniformly well attended.

Thirty papers were read in full during the course of the 2½ days, with 21 additional papers read by title. Three countries from outside North America were represented. Dr. Michael Schwartz of Copenhagen, Denmark, presented an excellent discussion of migraine as an allergic disease from a statistical point of view. A paper, "Effect of Cortisone on the Rise of Serum Antibody Level After the Injection of a Saturating Dose of Antigen in Rabbits," by Dr. Bernard N. Halpern, Prof. Pasteur Vallery-Radot and others of Paris, was read by Dr. S. M. Feinberg, it having been impossible for the authors to journey to America. A report, "Contribution to the Study of the Reticuloendothelial Origin of Dust Cells or Alveolar Macrophagi," by Dr. E. A. Pedace, Dr. A. E. Bachmann, and Dr. G. Ruiz-Moreno of Buenos Aires, was read by title, as time and the long program did not permit presentation in full.

A lively and crowded panel on ACTH and Cortisone was held Wednesday morning. It covered both physiologic and clinical aspects of the use of these new hormones as of the present.

Elvin A. Kabat, Ph.D., Associate Professor of Bacteriology, College of Physicians and Surgeons, New York, gave a masterly presentation Tuesday afternoon on the "Contributions of Immunology to the Study of Allergic Reactions." This was an experimental study of antigen-antibody relations.

Perhaps the most striking presentation of the entire program was the talk and motion pictures on "The Use of Tissue Cultures in the Study of Allergic Reactions" by Charles M. Pomerat, Ph.D., Professor of Cytology, University of Texas Medical School. Dr. Pomerat used actively growing human tissue cultures. Direct photomicrographs of groups of living cells in these cultures were obtained, single exposures on motion picture film being made at intervals of several minutes over periods of many hours. The films thus secured were projected at standard movie speeds, which represented a speeding up of the true rate of cell changes of about 600 times. Complete cycles of active mitotic cell division were shown in motion. The development of new cells and their active "nesting" in the conglomerate of older cells; pulsatile movements in cells and cell groups, in cell extensions and in intercellular fibrils, perhaps related to individual cell nutrition; cell diapedesis from circulatory channels; the rapid intercellular activity of "wandering" cells; phagocytosis and contractile vacuoles, contraction of sensitized cell groups on exposure to the specific antigen with

subsequent return to near normal; all were brilliantly demonstrated in motion. This new method would appear to open up an entirely new field in the study of cell physiology. Dr. Pomerat was accorded a tremendous acclaim by his audience.

The business session of the Academy was held on Tuesday afternoon, opened by President Baldwin's address in which he stressed the unity of the field of allergy and the need for more and better teaching of the subject in our medical schools. Reports of the Secretary, the Treasurer, and of several committees were read and adopted.

The Committee on the Constitution and By-laws with Dr. Theodore L. Squier as chairman had drawn up a number of amendments, which were presented, discussed, and adopted by vote of the Fellows. The significance of the more important of these will be outlined briefly.

The class of Affiliate Member in the Academy was abolished and a new class, Affiliate Fellow, was established. This new Affiliate Fellowship is broadly on a par with regular Fellowship, but is essentially honorary in character, carrying no dues or voting power, and not entitling the recipient to THE JOURNAL OF ALLERGY without charge. It is also directly comparable with Honorary Membership in allergy societies in Latin America, Europe, and elsewhere. Properly qualified physicians and scientists in America and abroad are eligible.

A class, Emeritus Member, was established to provide for any of our regular Members who apply for it before they are advanced to Fellowship.

In the future the provision of a photograph attached to the proposal blanks is made official. Letters of recommendation of sponsors will be sent by them direct to the Secretary of the Academy instead of being attached to the candidate's proposal blanks.

The sections on officers and the Executive Committee have been changed slightly. The office of President-elect has been newly created and will come into being in 1953. The Historian, who in the past has had the anomalous position of being an officer of the Academy but who sat on the Executive Committee without vote, has been made a voting member of the Executive Committee. The President-elect and the Historian thus increase the membership of the Executive Committee from nine to eleven.

The research activities of the Academy have been reorganized and simplified, with a new Coordinating Board of the Research Council established at the top to unify and coordinate the over-all activities of the Research Council and its several sections. The Committee on Therapy has been abolished as such, as its activities will be taken over by the appropriate section of the Research Council.

The Foundation for Allergic Diseases, an independent body comparable to the Infantile Paralysis Foundation and other organizations devoted to seeking funds for support of research, was established last

year on the initiative of the Academy. Its Board of Trustees will consist of physicians and laymen. The following were elected this year as initial physician-members of this Board: Horace S. Baldwin, Hal M. Davison, George Piness, S. M. Feinberg, Vincent J. Derbes, and Oscar Swineford, Jr. This Foundation will eventually stand alone, unconnected organically with any allergy or other society.

The International Committee rendered a brief report, a more detailed report having appeared in the November, 1951, issue of THE JOURNAL OF ALLERGY. Of importance to the Academy and to allergists the world over was the formal establishment of the International Association of Allergology in Zurich, Switzerland, in September, 1951. In March, 1951, the Executive Committee of the Academy charged the Academy's International Committee with studying the problem of participating in the formation of an international allergy association. After much correspondence and careful consideration, it was evident that the national allergy societies of the world were strongly in favor of such an association. The committee therefore recommended to the Executive Committee that the Academy join this proposed association. This recommendation was submitted by postal ballot to the Fellows of the Academy in July, 1951, who approved it by a practically unanimous vote. The Academy therefore has become an active member of the International Association of Allergology. By the latter's Constitution, every voting member of the Academy becomes a member of the I. A. A.

The following officers of the Academy were elected for the year 1952-1953:

President	Dr. Walter S. Burrage
Vice President	Dr. Ben Z. Rappaport
Secretary	Dr. Alan G. Cazort
Treasurer	Dr. Stanley F. Hampton
Historian	Dr. Howard Osgood
New Member on the Executive Committee	Dr. Carl E. Arbesman

The next annual meeting of the Academy will be held at the Statler Hotel, Boston, Mass., on Feb. 2, 3, and 4, 1953.

HOWARD OSGOOD, M.D.,
Historian

REPORT OF THERAPY COMMITTEE

A STUDY of Foralamin Fumurate was made by the Committee on Therapy of The American Academy of Allergy and the following comments and reports on the drug were submitted to the Academy at the Chicago Meeting, February, 1952. Following are the comments of the individual investigators of the drug and a summary of the results obtained.

Dr. Sidney Friedlaender: "The Foralamin tablets were distributed to 42 patients with seasonal or non-seasonal allergic rhinitis. Our impression concerning this drug is that it compares very favorably with Pyribenzamine, Neoantergan, and the other more active antihistaminics. As to side effects, these appear to be of the same order as those encountered with Pyribenzamine."

Dr. Edmund L. Keeney: "Actually, I see no reason for its (Foralamin) existence. It has nothing more to offer than any other antihistaminic compound on the market and as a matter of fact, does not compare with many of them."

Dr. Theodore B. Bernstein: "My results with Foralamin, and with the other antihistaminics as well, have not been very good."

Dr. Clarence Bernstein: "We found that Foralamin was, clinically, a potent antihistaminic and that in the usual dose as recommended it seemed to have a moderate soporific effect. We, therefore, found that it was more useful in those cases where nervous tension accompanied the allergic state or where we wished to have some hypnotic effect at a bedtime dose."

Dr. Carl E. Arbesman: "From the enclosed data and the remarks noted above, it would appear to us that Foralamin Fumurate is just another antihistaminic. It has nothing more to offer and in some cases less than other such drugs on the market. I, personally, would definitely not classify it with the most potent of antihistaminics or with the weakest. Its side effects are not too great. In occasional instances, I have found that Foralamin has been the best tolerated and most effective of antihistaminics in particular patients.

INCIDENCE OF SIDE EFFECTS IN 57 PATIENTS TREATED WITH FORALAMIN FUMURATE

SIDE EFFECT	NUMBER EFFECTED
Sleepiness	26
Nervousness	26
Jitteriness	
Insomnia	
Dizziness	20
Dryness of the Mouth	16
Headache	12
Lethargy	10
Palpitation	7
Nausea	6
Urinary Difficulty	4
Impotence	2
Constipation	1
Diarrhea	1
Aggravation of Symptoms	1

By in large, however, this was not the case. Dr. Theodore Bernstein of Evanston, Illinois, compared Foralamin with other antihistaminics in 30 patients. He found that it was most effective in only one patient; less effective in nine; and to some degree less effective in twenty patients. Each of these patients compared Foralamin with four other drugs.

SUMMARY OF CLINICAL EFFECTIVENESS OF FORALAMIN FUMURATE

CONDITION	NUMBER OF CASES	SLIGHTLY IMPROVED	SATISFACTORILY IMPROVED
Allergic Rhinitis (Seasonal)	86	18	37
Allergic Rhinitis (Perennial) Ext.	22	6	5
Allergic Rhinitis (Intrinsic)	6	4	1
Bronchial Asthma (Perennial) Ext.	6	0	2
Bronchial Asthma (Seasonal)	13	0	4
Urticaria	3	2	1
Atopic Eczema	3	0	0
Dermatitis (type?)	5	0	4
G-I Allergy	2	0	0
G-U Allergy	2	0	0
Total cases 148			

Announcement

Dr. Umberto Serafini, who will collaborate with Professor Di Mattei for the clinical section on the subject of drug allergy during the next Fifty-third Italian Congress of Internal Medicine, requests that readers of the JOURNAL send him reprints or references from their works on drug allergy. Those who have material are urged to send it to Professor Umberto Serafini, Largo della Gancia, 5 Rome, Italy.

Book Review

R for Medical Writing. By Edwin P. Jordan, M.D., and William C. Shepard, Philadelphia, W. B. Saunders Co., 1952, pp. 112.

The need for a book of this type is particularly apparent to editors of medical journals. The muddled expression, unsound statistics, and poor illustrations which actually appear in print represent only a small fraction of that submitted by authors. Too often enthusiastic haste to publish observations leads to neglect of the fundamental principles of clear presentation and even critical judgment of their significance. Strict adherence to the precepts of this book would improve at least nine-tenths of the papers offered to this journal.

This book concisely covers the preparation of a medical manuscript from the initial plan to the first revision with due attention to clarity, style, and intellectual honesty. Statistical methods, illustration, and proofreading are discussed in separate sections. It is recommended to all who wish to contribute to the medical literature.

Current Therapy, 1952. Edited by Howard F. Cohn, M.D., Philadelphia, W. B. Saunders Co., 1952, pp. 849.

This volume resembles in general its predecessor published last year although, as befits the increasing complexity of therapy, it contains more pages and represents the efforts of a larger group of experts. Much of the material is excellent but, as might be expected in a volume written by over 350 authors, there are many discrepancies which may confuse the general practitioner for whom the book is designed.

The section on allergic diseases is enlarged and improved by the addition of several outstanding contributors. Like other sections of the book it is written primarily for the general practitioner, but may also be helpful to the specialist in the field.

Prelude to asthma?

not necessarily . . .

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CONTENTS FOR JULY, 1952

(Continued from Front Cover)

Sudden Death from Bronchial Asthma Following Injection of Pyromen. C. H. A. Walton, M.D., and G. B. Elliott, M.B., Winnipeg, Canada 322

On the Rationale of Treating Allergic Diseases With Bacterial Pyrogens. Max Samter, M.D., and Martha A. Kofoed, B.S., Chicago, Ill. 327

The Use of a Closed System in the Study of Asthma and Emphysema. Francis C. Lowell, M.D., Irving W. Schiller, M.D., and Alice Lowell, M.D., Boston, Mass. 335

Influence of ACTH on Anaphylactic Shock in Guinea Pigs. R. Hoene, L. Coutu, A. Horava, J. Procopio, A. Robert and E. Salgado, Montreal, Canada 343

Anaphylactic Shock in the Pertussis-Vaccinated Mouse. Saul Malkiel, M.D., Ph.D., and Betty J. Hargis, B.S., Chicago, Ill. 352

Pharmacologic and Anaphylactogenic Properties of Staphylococcus Protein and Unfractionated Extract. Murray Dworetzky, M.D., Benjamin R. Zeitlin, M.S., Morton C. Kahn, D.Sc., and Horace S. Baldwin, M.D., New York, N. Y. 359

A Clinical Study of Phenacetin-Caffeine in the Treatment of Hay Fever. J. Richard Johnson, John M. Sheldon, Kenneth P. Mathews, and Robert G. Lovell, Ann Arbor, Mich. 365

Molds in House Dust, Furniture Stuffing, and in the Air Within Homes. Mary Ann Swaebly and Clyde M. Christensen, St. Paul, Minn. 370

A Study of Antibiosis Between Wind-Borne Molds and Insect Larvae from Wind-Borne Eggs. B. T. Griffith, Ph.D., Savannah, Ga. 375

Editorial

Fatal Allergic Reactions to Penicillin 383

Relationship Between Inoculations and Poliomyelitis 385

Book Review

Book Review 386

Announcement

Ragweed Pollen Survey 386

Erratum

President's Address. Horace S. Baldwin, M.D., New York, N. Y. (May, 1952, issue) 281

Allergy Abstracts

Abstracts *49-64*

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